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Archives of Internal Medicine

VOLUME 38 SEPTEMBER, 1926 NUMBER 3

THE OCCURRENCE OF BENIGN GLYCOSURIA IN DIABETIC FAMILIES *

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In later years investigations into heredity have steadily assumed a greater importance in medical research. The application of the results obtained by experimental work to the study of human disease entails, however, considerable difficulty. Agreement has not yet been reached regarding the question of heredity in diabetes mellitus. One view, held by Meulengracht [1] for one, is that the disease is dependent on a single dominant factor. Against this, Hansen [2] has asserted that it must be assumed that the disease is caused by several factors with a similar effect. He says, "The normal development of the pancreas is determined by several factors acting in a similar way. The severe cases of diabetes occur when many factors are lacking, the mild cases, when a few are lacking." Hansen [3] also expresses himself in favor of the view that there is a relation between diabetes mellitus and at least some of the mild glycosurias so commonly recognized in recent years by saying that "unser Wissen über die leichten Glycosurien in keinem Punkte dagegen spricht, dass sie alle—vielleicht mit Ausnahme der ganz vorübergehenden Fälle—auf einem geringen somatischen oder funktionellen Defekt in den Langerhansschen Inseln beruhen."

Investigations into heredity in diabetes are in certain respects attended by favorable circumstances, since the disease is common in almost every country, so that there will rarely be a lack of material that can form the basis of further investigations. In other respects we meet with a number of difficulties, some of which are common to all investigations into heredity, and others that especially apply to diabetes. The latter are connected particularly with establishing the diagnosis.

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* Contribution from the Medical Department B of the Rigshospital, University of Copenhagen (chief physician: Prof. Knud Faber).

* Given in an abbreviated form at Twelfth Scandinavian Congress for Internal Medicine, Stockholm, 1925.

1. Meulengracht, E.: Ugesk. f. Læger **86**:1 (June 3) 1925.
2. Hansen, Soren: Ugesk. f. Læger **86**:341 (April 17) 1924.
3. Hansen, Soren: Acta med. Scandinav. **62**:85, 1925.

In a large number of cases the disease is latent. Joslin [4] states that among his male patients above the age of 10, it was discovered by chance at an examination for life insurance in 11 per cent. Among forty-eight cases of diabetes discovered fortuitously I [5] found that in 77 per cent no diabetic symptoms of any kind were present at the time. Cases of this nature will easily escape detection, and if it is a question of persons belonging to an earlier generation one will be practically entirely prevented from acquiring any information about them.

Frequently the only thing known about one or more members of the family investigated is the bare fact that glycosuria is present. In such cases there is great uncertainty. The work of recent years has clearly shown the extraordinarily common occurrence of glycosuria whose relation to diabetes mellitus is either highly improbable (e. g., the "sweet soup" glycosuria described by me [6]) or at any rate doubtful.

Not uncommonly glycosuria is referred to as "sugar disease." In criticizing this we must take into consideration the fact that prior to the last few decades all spontaneous glycosuria, if it was not purely transient, was on the whole regarded as identical with diabetes mellitus, a view that cannot be endorsed now. It is true that some authors distinguish between the terms glycosuria and diabetes mellitus, but often the criteria for deciding whether a case shall be included in the one or the other group is not given. If one wants to be sure about these cases, therefore, it is necessary to select those in which the reason for the diagnosis is given. Three points especially come up for consideration: (1) the presence of the classical diabetes symptoms; (2) blood sugar determinations, and (3) the fatal course of the disease.

With regard to the first factor it must, however, be pointed out that there are already a number of reports in the literature [7] and one by me [5] of the occurrence of symptoms in glycosuria which cannot be regarded as definitely signifying diabetes mellitus. Thus, although in most cases the presence of these symptoms can be advanced as a good argument in favor of the diabetic nature of the glycosuria, they cannot constitute a certain proof in any particular case.

The blood sugar estimations are more reliable. In many cases these will not have been done because the routine investigation of the blood sugar has only become an established part of diabetic treatment in the

4. Joslin, E. P.: The Treatment of Diabetes Mellitus, 1917.

5. Holst, J. E.: Undersøgelser over lette Glykosurier, thesis, Copenhagen, 1924.

6. Holst, J. E.: Ugesk. f. Læger **84**:224 (Feb. 16) 1922.

7. Rolly and Oppermann: Biochem. Ztschr. **48**:200, 1913. Salomon, H.: Deutsche med. Wchnschr. **40**:217 (Jan. 29) 1914. Strouse, Solomon: Arch. Int. Med. **26**:751 (Dec.) 1920. Allen, F. M.; Wishart, Mary B., and Smith, L. M.: Arch. Int. Med. **24**:523 (Nov.) 1919. Motzfeldt, Ketil: Acta med. Scandinav. **57**:10 (Nov.) 1922. Hatlehol, Rolf: Blood Sugar Studies, Acta med. Scandinav., 1924, Supplement VIII.

last ten years. But even if such examinations are available the difficulties have not been disposed of, for opinion is divided as to how diabetes mellitus can be distinguished from nondiabetic glycosuria with their help. Salomon [8] and Rosenfeld [9] include some cases of hyperglycemia under the heading "diabetes innocens," while others do not regard the presence of normal fasting blood sugar as incompatible with diabetes mellitus.

The fatal course of the disease which affords a good basis for diagnosis is not always accessible as a not inconsiderable number of cases are recorded under other causes of death, such as gangrene and carbuncle.

Great difficulties are encountered through the usual lateness of occurrence of the disease. This assumes importance not only because some of the members of the family have died at an early age or, if they are still alive, have not yet reached the age when the disease most frequently appears, so that the possibility of a later occurrence cannot be passed over, but also because so many first get the disease at an age when the benign and therefore often undetected or wrongly diagnosed course is particularly frequent.

Even if the presence of typical diabetes mellitus is proved by the demonstration of glycosuria and the classical diabetes symptoms as well as the blood sugar determinations, we must convince ourselves that the cases included in this category cannot be regarded as forming an entity. Ever since von Mehring and Minkowski's [10] investigations it has been known that typical diabetes mellitus can be produced by removing or destroying a sufficiently large portion of the pancreas, just as there are many examples of diabetes occurring as the result of acute pancreatitis. Diabetes is thus not necessarily caused by special constitutional factors but may be of purely exogenous origin. We cannot exclude the possibility of such an exogenous origin in some of the cases of diabetes mellitus occurring as a result of chronic pancreatitis, arteriosclerosis with degenerative changes in the pancreas or other pathologic conditions.

In this connection it may be stressed that in the last few years since introduction of the insulin treatment cases of diabetes refractory to insulin have been reported by many authors, among them Strauss [11] and Umber and Rosenberg.[12] Among these, in addition to renal glycosuria, a number of cases of hyperglycemic glycosuria also occur, and these cases are interpreted by several authors as being of extra-insular origin.

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8. Salomon (footnote 7, second reference).
9. Rosenfeld, Georg: Berl. klin. Wchnschr. **53**:1093 (Oct. 2) 1916.
10. Von Mehring and Minkowski: Arch. f. exper. Pathol. u. Pharmakol. **26**: 371, 1889.
11. Strauss, H.: Klin. Wchnschr. **4**:491 (March 12) 1925.
12. Umber and Rosenberg: Klin. Wchnschr., 1925, p. 583.

At any rate, in some of these it must be pointed out, however, that the facts furnished are not so convincing that the authors' conclusions can be accepted as sufficiently well founded, but the possibility cannot be excluded that such cases of extra-insular diabetes may occur, even though, like the exogenous cases, they are only thought to constitute a small proportion of the total number of diabetes cases.

In view of the occurrence of such diabetes cases one should be careful not to draw any too certain conclusions from the scanty observations concerning the descendants of diabetic parents. What usually happens is that reliable information about some of the members of the family is forthcoming, while there are only scanty details about the others. When this is the case it must be realized that we cannot count on all the cases of glycosuria in a family being of the same kind. As time goes on, the reports of cases of benign glycosuria in diabetic families are getting more numerous. The oldest case, presumably, is that of Garrod [13] in 1913. He described a case of glycosuria in a girl of 10. It had lasted for two years, gave no subjective symptoms, was fairly independent of the diet and was associated with normal fasting blood sugar. The patient's brother, who was two years old, had typical diabetes mellitus with a considerable amount of hyperglycemia.

In 1914 the subject was discussed by Salomon,[8] who says: "Es ist öfters in der Ascendens des Diabetes innocens und renalis echter Diabetes zu vermerken." Other cases have been reported by Rosenfeld,[9] Johnson,[14] Hagedorn [15] and Hansen.[3]

Nothing definite can be said about the different cases reported by Begtrup,[16] Host [17] and others, since the diagnosis of diabetes mellitus cannot be regarded as having been established in these cases.

Quite recently Hatlehol [18] has discussed a number of cases. Among twelve families in which benign glycosuria occurred, diabetes mellitus also was present in five. The cases of glycosuria that occurred together with diabetes were partly cyclic renal and partly the so-called transition cases. In one family the father had diabetes mellitus while one child had a transition case and another a case of cyclic renal glycosuria.

Brugsch [19] also asserts that he observed diabetes and benign glycosuria in the same families. He says "Weiter ist in vielen Fällen des Diabetes innocens eine hereditär—familiäre Bindung mit dem echten Diabetes im Erbgange vorhanden. Man sieht also, auch der Diabetes

13. Garrod, A. E.: Brit. M. J., 1913, p. 850.
14. Johnson, A.: Acta med. Scandinav. **56**:485, 1922.
15. Hagedorn, H. C.: Undersøgelser vedrørende Blodsukkerregulationen hos Mennesket, thesis, Copenhagen, 1921.
16. Begtrup, E.: Ugesk. f. Læger. **78**:857 (May 25) 1916.
17. Host, H. F.: Meddelelse i det medic., Selskab i Kristiania, Sept. 26, 1923.
18. Hatlehol (footnote 7, sixth reference).
19. Brugsch, Theodor: Ztschr. f. ärtzl. Fortbildung., 1924.

innocens its ein Stück vom Diabetes mellitus." Last, Reiter [20] describes the occurrence of diabetes in association with cyclic hyperglycemia as well as with transition cases.

With regard to these earlier cases, however, it must be remarked that some of the authors themselves interpret them in another way than that given here; for instance, Salomon [8] and Rosenfeld [9] refer some cases of hyperglycemia to diabetes innocens.

Finally, I have myself observed diabetes mellitus and benign glycosuria in the same family a number of times. These cases are briefly reported below in connection with the genealogic trees. With respect to the diagnoses it should be stated that by diabetes mellitus is understood cases with fasting hyperglycemia while the term nondiabetic glycosuria embraces all cases of glycosuria in which the fasting blood sugar is normal without it being due to antecedent dietetic treatment.

GENEALOGIC TREES

The following signs are used in the genealogic trees in the accompanying illustrations: A square figure means a male; a circle, a female. Cases of diabetes are indicated by black, benign glycosuria by x in the figure denoting the sex. Cases of glycosuria in which the available information is insufficient for a certain diagnosis are indicated by horizontal shading.

Unfortunately the information about the families is sometimes rather meager, for in some of the cases only facts concerning the members who had glycosuria were obtainable. The first genealogic trees are examples of the simultaneous occurrence of diabetes and nondiabetic glycosuria among brothers and sisters.

FAMILY I

CASE 1.—A man, aged 42, at the age of 10 had lung disease. For some years he had had slight attacks of pain in the epigastrium, accompanied by nausea but without fever, vomiting or jaundice.

Glycosuria was demonstrated in 1907 (1 per cent) at examination for life insurance and was found several times subsequently.

In 1922 the patient was again investigated. He had not been dieted in the meantime, and did not exhibit subjective diabetic symptoms.

The fasting blood sugar was found to be normal and the urine gave a weak sugar reaction. After the administration of 68.5 Gm. of glucose (1 Gm. per kilogram) the fasting blood sugar rose at most to 0.166, and the rise was at an end in two hours.

CASE 2.—A woman, aged 39, had been treated in the hospital two years before this illness for typical diabetes mellitus. On admission 3 per cent sugar was found in the urine and 0.3 per cent in the blood.

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20. Reiter, P. J.: Undersøgelser over Sukkerstofskiftet ved Psychoser, thesis, Copenhagen, 1925.

FAMILY II. TWO CHILDREN WITH GLYCOSURIA

CASE 1.—A man, aged 38, had had glycosuria demonstrated in 1915 after he had felt weak for about a week, had lost weight and had had remarkably frequent and voluminous urination.

During his stay in the hospital in 1915 and 1916 there was continuous, slight glycosuria, the highest being 0.8 per cent on an unrestricted diet. The blood sugar curve after administration of 50 Gm. of white bread showed a normal rise.

Since 1916 glycosuria has steadily decreased and since 1921 could not be detected at all in spite of several examinations.

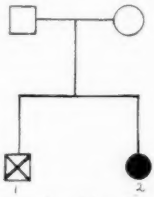

Fig. 1.—Families I and II.

In 1923 examination was made after the administration of 50 Gm. of glucose while fasting (patient's weight, 92 Kg.); before the administration the blood sugar was .0.097, it rose to 0.151 and after two hours, when the test was ended, it was 0.121. Slight glycosuria occurred during the test.

For several years the patient had not been dieted.

CASE 2.—The patient, a woman, died at the age of 37 in diabetic coma.

FAMILY III. THREE CHILDREN WITH GLYCOSURIA

CASES 1 and 2.—A boy and a girl both died at the age of 11 in diabetic coma.

CASE 3.—A man, aged 24, had glycosuria demonstrated in 1913 at several examinations but it disappeared spontaneously in a short time. He had not been dieted since and exhibited no subjective typical symptoms.

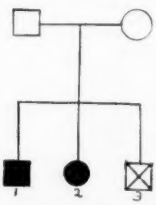

Fig. 2.—Family III.

In 1922 examination was made after the administration of 52.5 Gm. of glucose (1 Gm. per kilogram) while fasting. Before administration the blood sugar was 0.086, it rose to 0.189 and after one and three fourths hours was 0.088. Slight glycosuria occurred during the test.

FAMILY IV. GLYCOSURIA IN FATHER AND TWO CHILDREN

CASE 1.—In this patient, a male, glycosuria was demonstrated on only one occasion.

CASE 2.—The patient, a boy, died at the age of 16 in diabetic coma.

CASE 3.—A man, aged 23, in 1916 had glycosuria demonstrated at repeated examinations made on account of weakness and loss in weight. During nine days' stay in the hospital shortly after, the glycosuria could not be detected. Two blood sugar examinations gave 0.116 and 0.102.

In 1925 the patient felt well and had no signs of diabetes.

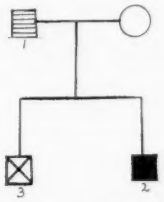

Fig. 3.—Family IV.

FAMILY V. THREE CASES OF GLYCOSURIA

CASE 1.—A woman died from diabetes at the age of 70.

CASE 2.—A man, aged 21, had glycosuria detected in January, 1923, at an examination on account of weakness. At frequent examinations subsequently the fasting blood sugar was always normal.

After administration of 64 Gm. of glucose (1 Gm. per kilogram) while fasting the blood sugar rose to 0.175 and the rise was at an end in one and one-half hours. Slight glycosuria occurred during the rise. After taking 50 Gm. of white bread, the blood sugar rose to 0.135 without glycosuria.

CASE 3.—A woman, aged 23, for two years had typical diabetes mellitus with fasting hyperglycemia. She is now having insulin treatment.

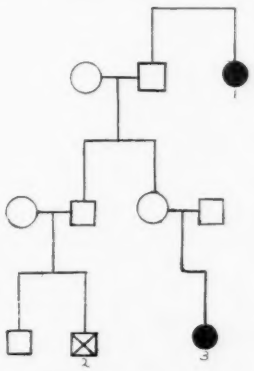

Fig. 4.—Family V.

FAMILY VI. FOUR CASES OF GLYCOSURIA

CASE 1.—A male died of diabetes.

CASE 2.—The patient, a man, was treated in 1915 in the hospital for "sugar disease." The urine contained only a small quantity of sugar; symptoms of mild diabetes, thirst, polyuria, etc., were present. He is now said to be healthy.

CASE 3.—Glycosuria was demonstrated in the patient, a woman, in 1921. At a single examination then, 3 per cent sugar was found in the urine while numerous subsequent examinations on an unrestricted diet have always given a negative reaction.

CASE 4.—A woman, aged 40, had examinations in 1907 and 1908 on account of salpingitis; the urine was found free from sugar. Glycosuria was detected in 1910 at an examination on account of thirst, lassitude and loss in weight (16 Kg. in eighteen months).

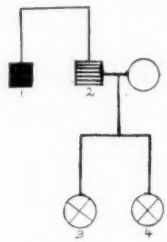

Fig. 5.—Family VI.

On admission to the hospital the urine gave a positive reaction for sugar, acetone and diacetic acid; the patient was dull and drowsy and the condition was regarded as incipient diabetic coma. The acidosis, however, disappeared quickly; the glycosuria persisted somewhat independently of the diet.

The patient was later treated in the hospital in 1912, 1914, 1915, 1917, 1921 and 1923.

At many examinations during the last five terms of hospital treatment, a normal fasting blood sugar was always demonstrated. In 1923 examination was made after the administration of 50 Gm. of glucose while fasting. Before the administration the blood sugar was 0.088, it rose to 0.195 and was again normal in two hours.

During each visit to the hospital the urine contained sugar, usually even while fasting.

At the last admission rather pronounced acidosis was found as in 1910 and, just as at that time, the patient appears to have been diagnosed as a case of threatening coma. During this visit, however, the acidosis also disappeared rapidly.

Dietetic treatment was carried out only periodically.

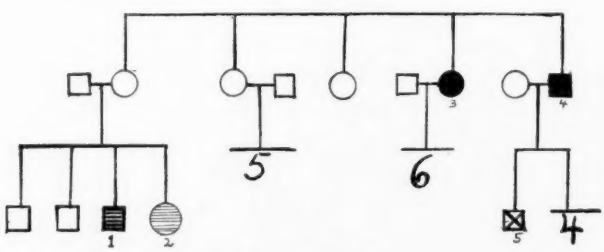

Fig. 6.—Family VII.

FAMILY VII. FIVE CASES OF GLYCOSURIA

CASE 1.—A man, aged 55, for some years had glycosuria without subjective typical symptoms.

CASE 2.—A woman, aged 65, had the same condition as patient 1 of this family group.

CASE 3.—A woman died from diabetes at the age of 76, after thirteen years of typical illness.

CASE 4.—A man died from diabetes at the age of 65. He had had the disease for a year or two.

CASE 5.—A man, aged 45, had marked glycosuria demonstrated in April, 1922, and again in June, 1923. Two blood sugar examinations showed normal fasting blood sugar.

In June, 1923, the patient was examined after the administration of 50 Gm. of glucose. The blood sugar before administration was 0.093, it rose to 0.189 and was normal again in two hours. Slight glycosuria occurred during the test.

In the following cases glycosuria occurs in several generations.

FAMILY VIII. FOUR CASES OF GLYCOSURIA

CASE 1.—A woman, aged about 60, suffered from typical diabetes mellitus with considerable hyperglycemia.

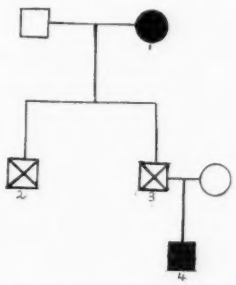

Fig. 7.—Family VIII.

CASE 2.—A man, aged 34, had glycosuria demonstrated in 1910 and several times later, the highest being 1 per cent. He had no subjective typical symptoms. The patient avoided sugar but otherwise took a normal diet.

At three blood sugar examinations in 1922 normal values were found.

CASE 3.—A man, aged about 28, had glycosuria for four or five years without subjective symptoms. No information about blood sugar examinations was available.

CASE 4.—A boy died in typical coma at the age of 2.

FAMILY IX. FOUR CASES OF GLYCOSURIA

CASE 1.—A male died of diabetes.

CASES 2 and 3.—Two males suffered from "sugar disease." No further details were given.

CASE 4.—A man, aged 30, had glycosuria demonstrated in 1915 at an examination for life insurance, and several times afterward, always a small amount. The patient avoided sugar but otherwise took a normal diet. The fasting blood sugar and the rise after the administration of glucose were normal at several examinations (after 50 Gm. of glucose the highest value being 0.17). The last examination was in 1922.

FAMILY X. SEVEN CASES OF GLYCOSURA

CASES 1 and 2.—Two males died of diabetes.

CASE 3.—A girl, aged about 12, suffers from diabetes gravis but is now under insulin treatment.

CASE 4.—A man died at the age of 72 of cancer of the liver. He had glycosuria from age of 46 but no further details about it were obtainable.

CASE 5.—A man, aged 60, had diabetes for twenty-five years with as much as 8 per cent sugar in the urine and considerable hyperglycemia.

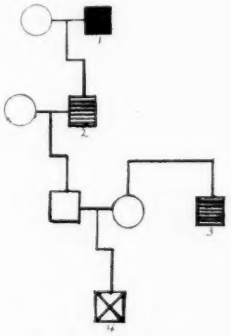

Fig. 8.—Family IX.

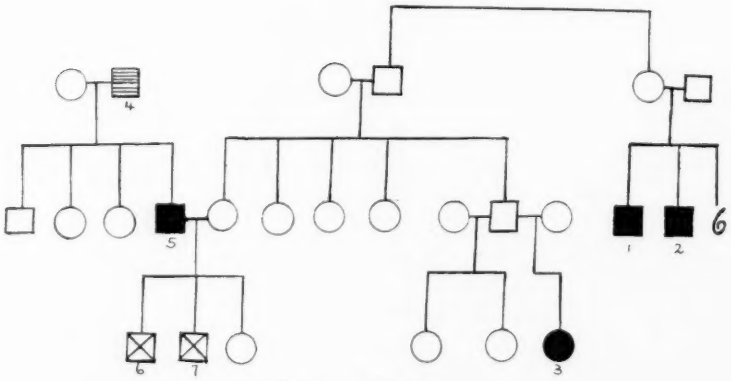

Fig. 9.—Family X.

CASE 6.—A man, aged 31, had glycosuria demonstrated in 1917 and many times after. The patient avoids sugar but otherwise does not diet himself now, though earlier he did so periodically.

No diabetic symptoms were noted. The fasting blood sugar on repeated examinations was always normal.

In 1922 a test was made after the administration of 75 Gm. of glucose (1 Gm. per kilogram). Before administration the blood sugar was 0.103, afterward it rose to 0.24 and was normal again in one and one-half hours. At two threshold examinations sugar excretion occurred with a rise to 0.149 but not with a rise to 0.126.

Another examination for glycosuria in 1923 gave practically the same result.

CASE 7.—A man, aged 28, was examined in December, 1924, a few days after glycosuria was demonstrated. Glucose, 71 Gm. (1 Gm. per kilogram), was given. Before the administration the blood sugar was 0.092, afterward it rose to 0.165 and was normal again in an hour. At the threshold determination marked sugar excretion was found with blood sugar rise to 0.145.

FAMILY XI. EIGHT CASES OF GLYCOSURIA

CASE 1.—A man died of diabetes at the age of 36.

CASE 2.—A girl died in diabetic coma at the age of 6.

CASE 3.—A woman, aged 20, had glycosuria demonstrated in 1920 in connection with diphtheria and several times afterward, always slight. She never dieted, and felt perfectly well. In 1923 examination was made after the administration of 50 Gm. of glucose. Before administration the blood sugar was 0.098, afterward it rose to 0.15 and was normal again in one and three-fourths hours. There was slight excretion of sugar during the test.

CASE 4.—A man, aged about 50, had glycosuria for twenty years without subjective symptoms.

CASE 5.—A man, aged about 45, had glycosuria for "many years" without subjective symptoms.

CASE 6.—A man, aged 47, had glycosuria from the age of 18. At that time he is said to have had from 10 to 12 per cent sugar in the urine and to be "at the point of death." He now feels perfectly well.

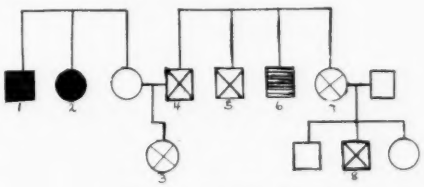

Fig. 10.—Family XI.

CASE 7.—A woman, aged about 50, had glycosuria on and off for twenty-nine years. She avoided sugar but otherwise took a normal diet. Examination of the fasting blood sugar in 1917 gave a normal result.

CASE 8.—A man, aged 29, had glycosuria demonstrated in 1914. Many examinations were made in 1914, 1917, 1919, 1923 and 1924 of the fasting blood sugar and the rises after glucose administration always gave normal results. Glycosuria was often present while the patient was fasting. For several years the patient has not been dieted.

In order to give the right impression of the frequency with which orthoglycemic glycosuria and diabetes mellitus occur in company with one another, I must also state that besides the cases referred to here I have observed a considerable number of families in which the same association seems to occur. I have not included these, however, because there are so many gaps in the information and examinations that the individual cases could not be judged with the requisite accuracy.

If my observations are taken with the earlier pronouncements, especially of Salomon, Brugsch and Hatlehol, I do not believe it will be possible to look on the simultaneous occurrence of diabetes mellitus and nondiabetic glycosuria in the families as fortuitous; the frequency seems to be too great.

Like earlier authors I have found that the cases of glycosuria occurring in diabetic families do not belong to definite types but that cases due to alimentary hyperglycemia as well as renal forms and transition cases are found. In one instance I found in the father and two sons of the same family three different forms of glycosuria; diabetes mellitus, glycosuria with alimentary hyperglycemia and alimentary renal glycosuria (family X). This corresponds to a case in one of the families described by Hatlehol.

The detection of the association of diabetes and nondiabetic glycosuria is important in several different ways. From a purely practical standpoint it greatly emphasizes the necessity for blood sugar examinations as a necessary element in the investigation of a case of glycosuria even when other cases in the family provide weighty evidence for regarding it as either diabetic or innocent.

Furthermore, these observations possess great theoretical interest both for the question of heredity in diabetes and for the limitation of the term diabetes mellitus. But they can hardly be used in support of any of the views advanced concerning the heredity of the disease. As mentioned above Søren Hansen has held that the different forms of glycosuria, from the mildest to the most severe diabetes, differ only quantitatively, the mild forms depending on the absence of a few and the most severe on the absence of many of the factors concerned in the occurrence of diabetes. A sharp distinction between mild and severe diabetes cannot be drawn; however, a mild case can develop into a severe one. If, therefore, orthoglycemic glycosuria was only quantitatively different from actual diabetic glycosuria we should expect to see the development of orthoglycemic into hyperglycemic forms more frequently, for one good reason that the former have often had absolutely no treatment. But such a transition, as I have shown,[5] occurs extremely rarely, if it can be regarded as having been definitely demonstrated at all.

If, therefore, it is contended that diabetes is caused by a plurality of factors and that at the same time there is an hereditary connection between diabetes and orthoglycemic glycosuria, it seems more reasonable to assume that there are several differently acting factors, some of which are specific for diabetes mellitus while others are common to it and orthoglycemic glycosuria. The conception, defended principally by Meulengracht, that diabetes is caused by a single dominant factor is not supported by the present observations although they are not incompatible with this hypothesis. The question is hardly ready to be definitely settled, but the increasing frequency with which the association of diabetes mellitus with benign glycosuria is observed makes it worth while further to investigate this subject with more extensive material.

SUMMARY

1. In eleven families, described here, both diabetes mellitus and nondiabetic glycosuria occurred.

2. The glycosuria occurring in the diabetic families was of no definite type but comprised cases due to alimentary hyperglycemia as well as the renal form.

3. The association of diabetes and nondiabetic glycosuria was observed so frequently that it could not be fortuitous, but must have depended on an hereditary biologic relationship.

4. The restricted extent of the material did not permit definite conclusions to be drawn concerning the nature of this relationship, but it seemed hardly likely to be due entirely to a quantitative difference.

PERNICIOUS ANEMIA, ACHYLIA GASTRICA AND COMBINED CORD DEGENERATION AND THEIR RELATIONSHIP *

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The first description of idiopathic anemia by Addison in 1855 and the subsequent work in 1872 by Biermer, who coined the term pernicious anemia, contained no mention of achlorhydria or combined cord degeneration. It was not until 1866 that Cahn and von Mehring [1] first discovered the absence of free hydrochloric acid in the gastric juice in a case of pernicious anemia. Since then the relationship of achlorhydria and pernicious anemia has been recognized and of late has been the subject of considerable conjecture.

I propose to consider here this association of the gastric anacidity, the cord changes and the anemia, and it is hoped that by a survey of the literature and the study of some new material that the important known facts in this relationship may be summarized.

The absence of free hydrochloric acid in the gastric contents of pernicious anemias has been reported to be 100 per cent by Ewald,[2] Zadek [3] and Weinberg [4] in a large series of cases. In this country Levine and Ladd [5] at Johns Hopkins Hospital found in 150 cases only three with a normal amount of acid. At necropsy one of these cases was confirmed, the other two not certainly addisonian. Five cases with free hydrochloric acid, with a doubtful blood picture, proved to be not pernicious. Hurst and Bell [6] in 1922 found that sixty-four of sixty-six cases had total anacidity, and in 1925 found thirty-six analyzed cases to be achlorhydric. On the other hand, MacBride and Carmichael [7] report that fourteen cases out of fifty-five had free hydrochloric acid; four of these were examined at necropsy and the diagnosis was definitely proved.

I have analyzed the hospital histories of a series of seventy-four cases of pernicious anemia and found only three cases with free acidity:

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* From Cook County and Wesley Memorial Hospitals.
* Read before the Chicago Society of Internal Medicine, Jan. 15, 1926.

1. Cahn, A., and von Mehring, J.: Deutsches Arch. f. klin. Med. **39**:233, 1886.
2. Ewald; Kraus, and Brugsch: Spec. Path. u. Therap. **8**:1216, 1920.
3. Zadek: Schweiz. med. Wchnschr. **51**:1087, 1921.
4. Weinberg: Deutsches Arch. f. klin. Med. **124**:447, 1918.
5. Levine, S. A., and Ladd, W. S.: Bull Johns Hopkins Hosp. **22**:254 (Aug.) 1921.
6. Hurst, A. F., and Bell, J. R.: Brain **45**:266 (Oct.) 1922.
7. MacBride and Carmichael: Proc. Roy. Soc. Med. (Neurol. Sec.), 1925.

SUMMARY OF FINDINGS

CASE 1.—A man, aged 36, complained of generalized weakness and dyspnea for one year. His skin was lemon colored. The red blood cells totaled 2,016,000, the white blood cells 3,200, and hemoglobin 43 per cent. There were many megaloblasts and normoblasts and macrocytes in the blood smear. A fractional test meal revealed free hydrochloric acid 30, total 70. Roentgen-ray examination was negative. No other cause for the anemia was found.

CASE 2.—A man, aged 49, complained of loss of weight and gastric distress for six months. The red blood cells totaled 3,144,000, hemoglobin 40 per cent, white blood cells 5,800, free hydrochloric acid 30, total 60. A blood smear revealed abnormally large cells. Physically and roentgenologically there was no other cause for his condition.

CASE 3.—A woman, aged 42, who complained of dyspnea for two years, developed lemon colored skin and loss of weight. The blood count at entrance was red blood cells 4,500,000, hemoglobin 55 per cent, free hydrochloric acid 30, total acid 60. Nothing else was found. During two months in the hospital she developed tingling and numbness in the legs and then presented the objective neurologic signs of subacute combined cord degeneration.

It should be stated just what clinical criterion should be adopted for the diagnosis of pernicious anemia. Certainly the subjective and objective symptoms are too variable and are not specific for the disease. The blood count is often misleading, nucleated cells are inconstant, and the color index may be above or below 1 in secondary or pernicious anemia. The constant sign in Addison's anemia is the great variation in size of the red cells, yet the average size is greater than normal. Price-Jones [8] has introduced an accurate method of charting this fact. He measures carefully 500 cells and records the number of cells of each size. He charts these on a graph, the abscissa representing the number and the ordinate the size in microns. Normal blood cells are between 4.7 and 9.5, averaging 7.2 microns. In pernicious anemia the cells vary from 3.7 to 13.9, averaging 8.3 microns. This makes a curve with a broad base and far to the right.

The achlorhydria of pernicious anemia is characterized by its completeness and invariability. It is present throughout the course of the disease and the remissions have no effect on it. The hemoglobin may return to 90 per cent but the anacidity persists. It is, in fact, present in most cases, no matter how recently the initial symptom appeared. This is contrasted with carcinoma of the stomach, in which the achlorhydria is progressive and never constantly complete. Achlorhydria may be known to be present months or even years before the recognition of the anemia. These cases are, however, not common. Faber reports anacidity preceding the anemia by ten years. Hurst has seen an interval of twelve years, Sturtevant [9] fourteen years, and Riley [10] twenty-five

8. Price-Jones, C.: J. Path. & Bacteriol. **25**:487 (Oct.) 1922.

9. Sturtevant, M.: Achlorhydria Preceding Pernicious Anemia; Case of More Than Fourteen Years' Duration, J. A. M. A. **85**:1638 (Nov. 21) 1925.

10. Riley, W. H.: Achlorhydria Preceding Pernicious Anemia, Correspondence, J. A. M. A. **85**:1908 (Dec. 12) 1925.

years. In 150 cases Levine and Ladd found only three in which the anacidity preceded the disease. In two cases the interval was less than a year, and one of six years. No other type of anemia is associated with achlorhydria, the most severe secondary anemias usually revealing normal gastric contents.

It is known that even without a gastric analysis before the onset of the disease, the history often elicits the fact that gastro-intestinal symptoms have preceded the hospitalization of the patient by some months. Bramwell [11] in 1899 found that diarrhea often preceded the anemia and thought the previous diarrhea was evidence of an intestinal infection causing the anemia. In this series of cases I found that three patients had complained of gastro-intestinal symptoms all their lives. In addition one man, aged 60, had gastric upsets for the forty-five years preceding, one man for nine years, one girl, aged 24, had spells of nausea for seventeen years, and one patient had distress for twelve years. Thus, in seventy-four cases there were seven, or 9 per cent, with a previous history of gastro-intestinal upsets—a number much too low from which to draw conclusions. Eighteen patients complained of gastro-intestinal symptoms as the initial symptom and another twenty-eight developed some type of distress during the course of the disease. Twenty-three, or thirty per cent, of the patients had no subjective symptoms of this type throughout the course of the disease, although all but two of these had complete anacidity. MacBride and Carmichael report that 55 per cent of their female and 74 per cent of their male cases had no gastro-intestinal symptoms prior to the onset of the disease.

Hurst concludes from these uncommon cases that achlorhydria precedes the development of pernicious anemia and must, therefore, be a predisposing factor. He believes that any focus of infection, such as the teeth, sinuses or tonsils, discharging into the alimentary tract may result in an intestinal infection. This takes place because the antibactericidal action of the acid is lost. It has been shown that concentrations of hydrochloric acid as found in the stomach during digestion are sufficient to kill cultures of streptococci. The infection then results in the absorption of toxins which presumably have two components. One is hemolytic and causes excessive red cell destruction and at the same time acts on the bone marrow, resulting in the formation of excessively large cells. The other component is a neurotoxin and is the cause of the spinal cord degeneration. It is believed that the marrow is eventually exhausted by the continual hemolysis and that immature nucleated reds are then thrown into the blood stream. During remissions the bone marrow becomes rejuvenated and is able to cope with the hemolysis, the nucleated reds disappear, but the large cells

11. Bramwell: Anemia and Other Disorders, New York, Macmillan Company, 1899.

persist since they are a result of the ever present toxin. The remissions are supposedly due to an increase in bodily resistance to the toxin, which, however, is never complete; therefore, relapses appear.

To prove that there is present an intestinal infection Hurst had cultured the duodenal contents and finds in every case of pernicious anemia *Streptococcus longus* of the hemolytic type, while in normal persons streptococci were present in 11 per cent, but these were never hemolytic. In a later article, from 70 to 80 per cent of the anemias were positive while no streptococci were found in the controls. Vaccines of this organism were supposed to cause almost complete remissions; however, no details are given as to how the frequently found lengthy remissions are excluded.

Kopoloff's [12] work is contradictory. He finds no difference in the bacterial content of aspirated material in a large series of normal persons and of patients having definite oral infections. Streptococci were present in about the same percentage in both series. Streptococci were found as often with low as with high gastric acidity.

Persons with anacidity should be predisposed to pernicious anemias, as the largest number of such patients are persons having achylia gastrica. Martius has shown that these patients show no anatomic change in their gastric mucosa, but are suffering from a constitutional inborn defect of the secretory power of morphologically normal glands. In favor of this is its familial occurrence in persons with or without gastro-intestinal symptoms. Albu, Udamonda and Jung have found achylia in more than one member of the same family. Children as young as 4 years have been seen with this condition. Bennet and Ryle [13] found that four out of 100 medical students had achylia. Its early appearance suggests that not only may it be familial but that it may also be congenital. Thus, Hurst explains those relatively rare cases of pernicious anemia occurring in families, believing that they are a result of familial achylia. Among others Patek [14] reports five cases of pernicious anemia in one family, all without gastric symptoms. Bartlett [15] has seen five cases in a family of eight, all having had bilious attacks since childhood. Levine and Ladd found nine in 150, or 6 per cent, to be familial. I am only able to find one case in the seventy-four giving a familial history.

12. Kopoloff: Arch. Neurol. & Psych. **8**:1-93, 1922.
13. Bennet, T. I., and Ryle, J. A.: Guy's Hosp. Rep. **71**:286 (July) 1921.
14. Patek, A. J.: Family Pernicious Anemia, J. A. M. A. **56**:1315 (May 6) 1911.
15. Bartlett, C. J.: Family Pernicious Anemia, J. A. M. A. **60**:177 (Jan. 18) 1913.

CASE 4.—A woman, aged 41, had diarrhea since the age of 14 years; she had had a breakdown for seven years during which she was always exhausted. The diarrhea became severe three years before admission. There were paresthesias and numbness in her legs. The patient was very intelligent and before knowing the diagnosis stated that she feared pernicious anemia because an aunt and uncle had both died of this disease.

In some families anemia has been associated with achylia in other members. Queckenstedt, Weinberg and Hurst report such cases. I find one case suggestive of this.

CASE 5.—A man, aged 52, had stomach trouble since he was a baby. He had vomiting spells for years and always had diarrhea. He stated that his two children had exactly the same gastric distress since childhood. He had the typical findings of pernicious anemia and no free hydrochloric acid.

Certainly the presence of achylia in the families of a few patients is not evidence enough to prove a causal relationship. It may be purely casual.

If the hydrochloric acid were a barrier against infection then achylia patients should be liable to any sort of infection. On going over twelve available patients with achylia, one of whom had a daughter with the same condition, I was impressed with the frequency of infections. One had gallbladder disease, four had chronic rheumatoid arthritis, and two had infections of the colon. The other five had gastrointestinal symptoms only.

The other anacidities should also be expected to predispose to anemia. Accordingly, Hurst cites two cases of alcoholic gastritis with anacidity and typical addisonian anemia confirmed at necropsy. Wakefield described a case of carcinoma of the stomach and achlorhydria in which the necropsy revealed in addition the picture of pernicious anemia. Garvey and Stern [16] have seen a similar case. The association of gastrectomy and gastro-enterostomy with the development of anemia is remarkable. Both of these operations produce essentially an achylia.[17] Conybeare and Willcox have seen pernicious anemia develop after gastroenterostomy, and Hartman [18] from the Mayo clinic describes a patient who two years after a total gastrectomy developed addisonian anemia, due, he concludes, to the postoperative achylia. Moynihan saw pernicious anemia develop three years and eight months after a gastrectomy for cancer of the stomach. However, Lewisohn and Feldman definitely mention in reporting a large experience in gastrectomies for the last five years that they have never seen anemia appear. With so few

16. Garvey, J. L., and Stern, L. D.: Am. J. M. Sc. **168**:847 (Dec.) 1924.
17. Willson, R. N.: The Spinal Cord in Pernicious Anemia, J. A. M. A. **59**:767 (Sept. 7) 1912.
18. Hartman, H. R.: Am. J. M. Sc. **162**:201 (Aug.) 1921.

cases in the literature, postoperative anemia, as well as that occasionally developing in the course of other diseases, must be considered as a coincidental development of pernicious anemia.

As to the source of the infection, Hurst states that he has never seen a case of pernicious anemia without oral or pharyngeal sepsis, under which he includes glossitis. That the glossitis is an infection is doubtful and rarely does it appear until the onset of the disease. It has also been seen in the secondary anemia of bowel carcinoma.

MacBride and Carmichael vigorously reject the gastro-intestinal theory because 55 per cent of the females and 74 per cent of the males of their cases had no gastro-intestinal symptoms whatsoever before the anemia was definitely established. These authors have noticed that 96 per cent of the females had a myxedematous appearance and had ceased menstruating two years before the onset of the disease. This led them to consider an endocrine disturbance as the basis of the disorder. I find the average age of anemia patients coming to a hospital to be 49 years, 88 per cent appearing in or after the fourth decade of life; furthermore, the average time between the first symptom and hospitalization was two years. It is no wonder then that menstruation should have ceased at least two years before the onset and this is no evidence to regard its occurrence as an etiologic factor.

This is a summary of our knowledge regarding the relationship of anacidity to pernicious anemia. The theory that anacidity is a predisposing factor in the production of the anemia rests on slender foundation. I found one patient who had vague symptoms of weakness seven years before it became necessary for her to have medical attention. It must be remembered that pernicious anemia may exist as a disease entity long before the typical symptoms develop. When anacidity is found in such cases it should not be interpreted as an etiologic factor but as the first sign of the disease. Only a few isolated cases of achylia definitely preceding the anemia by many years can be found, and in many series, including my own, a few cases are recorded in which the anemia was accompanied by normal acidity.

Achylia patients are apparently prone to infections, particularly arthritis. But arthritis also attacks many persons with normal gastric juice. With rare exceptions anacidity and pernicious anemia are associated. An infection of a nonspecific streptococcus should take place by other routes than the intestinal tract and thus appear as the arthritides do, for example, in people with normal acidity. The large number of cases with gastric symptoms only after the onset of the anemia suggests that the anacidity is part of the disease picture of pernicious anemia. The argument that the anemia itself does not produce achlorhydria because severe secondary anemias have normal acidity may be answered by the fact that a secondary anemia with as low a red count as in

pernicious anemia is an acute condition and that the patient either dies or recovers in a relatively short time, while the average addisonian anemia patient has the disease for two years even before hospitalization.

Furthermore, the hypothetic streptococcus hemolytic intestinal infection must be one without pathologic changes in the intestinal tract. In view of the virulent general effect of this organism, which is not a normal inhabitant of the bowel, it seems unlikely that it may exist for so long without causing local lesions. It also is unlikely that a congenital predisposing factor should be present in 88 per cent of cases for more than forty years before the development of the disease.

Since Lichtheim and Minnich first described subacute combined degeneration of the cord associated with pernicious anemia, the two diseases have been considered to have an intimate relationship. Nonne [19] at first considered the pathologic condition of the cord to be a result of the anemia, but being unable to find cord changes in the secondary anemia patients that he examined, came to the view that the anemia and cord degeneration are due to the same toxic agent. Hurst [20] believes that pernicious anemia is due to toxic substances composed of a neurotoxin and a hemolytic toxin which vary in their relative quantities. If the neurotoxin preponderates, cord degeneration is in the foreground and may develop and persist for some time before the anemia appears. I found one case in which the cord degeneration apparently preceded the anemia by four years.

CASE 6.—A man, aged 58, had a spastic paraplegia with incontinence of urine for four years. He was unsteady on his feet and complained of tingling pains in the legs. During the four years he had been treated for tabes. In the hospital he was lemon colored, with less than a million red blood cells and 30 per cent hemoglobin; the blood smear was typical of pernicious anemia. Deep sensation and deep reflexes were absent in the legs.

If the anemia never appears the hemolytic toxin is supposedly in abeyance but is always potentially present. If anemia develops during the disease it is always primary and, according to Hurst, some cases are diagnosed as secondary because the size of the red cells has not been observed. Bramwell believes that the severe anemia may appear suddenly a short time before death in cases that before had a normal blood picture. He finds that the blood change produces a quick reversal from spastic to flaccid paralysis. Hamilton reports a case in which a remission was accompanied by the entire disappearance of objective sensory changes, which returned shortly before death. Usually the remissions have no effect on the nervous symptoms. In my series there is not one example of such improvement.

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19. Nonne: Deutsche Ztschr. f. Nervenh. **6**:313, 1895.
20. Hurst: Brain **48**:155, 1925.

Hurst has found in sixteen cases of cord degeneration achlorhydria in 100 per cent. Vanderhof [21] found twenty-nine cases with anacidity. However, the cases of both authors were probably associated with pernicious anemia, and are not conclusive evidence that combined cord degeneration of any etiology is associated with anacidity. Hurst states that in three cases in which the tentative diagnosis of posterolateral sclerosis was made and free acid was found in the stomach, later developments proved the patients to be syphilitic.

The argument has been advanced that the familial combined cord degeneration, which is a rare occurrence, like the familial pernicious anemia is a result of familial achylia. But Oppenheim [22] has pointed out that these cases are in reality familial pyramidal degeneration, an altogether different disease and definitely hereditary.

The percentage of anemia patients developing cord degeneration has been variously stated. Dana [23] puts the number at 10 per cent; Taylor, 12 per cent; Bramwell,[24] 2 per cent; Nonne, 2 per cent; McCrae,[25] 25 per cent; Hannenberg, 50 per cent; Hurst, 70 per cent, and Woltman [26] finds indisputable evidence of involvement of the nervous parenchyma in 80 per cent of their cases. What these last two observers have adopted as the clinical criterion of cord involvement is of importance. Hamilton [27] has clearly shown that objective and subjective neurologic signs may be present in patients who reveal post mortem no demonstrable changes in the central nervous system. These cases, however, by Marchi and Weigert stains reveal evidences of a mild peripheral neuritis which differs in no respect from that seen in other toxic conditions. It is rare to see a severe secondary anemia patient with a red blood cell count as low as the usual pernicious anemia without the presence of tingling and numbness, which usually are not associated with cord degeneration. These paresthesias caused by any type of anemia should be attributed to changes in the peripheral nerves. I therefore cannot accept, as has Woltman, that tingling and numbness are diagnostic of central nervous system involvement. Definite objective neurologic signs, such as reflex and sensory changes due to lesions of the long root fibers of the posterior columns, are used in this series as evidence of cord involvement.

On going over the seventy-four cases I find that fifty-two patients, or about 70 per cent, complained of tingling, numbness, coldness in the extremities or sensations of pins and needles. Thirty per cent had no

21. Vanderhof: Arch. Clin. Med. **22**:958, 1922.
22. Oppenheim: Lehrbuch der Nervenkrankheiten, Karger, Berlin, 1923.
23. Dana: J. Nerv. & Ment. Dis. **16**:205, 1891.
24. Bramwell: Brit. M. J. **1**:1306, 1910.
25. McCrae, Thomas: Pernicious Anemia, J. A. M. A. **38**:148 (Jan. 18) 1902.
26. Woltmann, H. W.: Am. J. M. Sc. **157**:400 (March) 1919.
27. Hamilton and Nixon: Arch. Neurol. & Psychiat. **6**:1 (July) 1921.

subjective sensory complaints and none of these developed combined cord degeneration. Of the fifty-two who had subjective sensory changes only twenty-four developed combined cord degeneration. My figure is therefore 30 per cent of the total.

In classifying the initial symptoms of the patients I found that diarrhea was the first sign in six cases, two of which had cord changes; pain in the abdomen in two, with no cord changes; dyspnea in seven, two of these having a pathologic condition of the cord; pallor in four cases, one having cord degeneration; loss of weight in five, with one cord degeneration, and weakness was the first symptom in twenty-six patients, of whom seven had combined cord disease. Nausea and vomiting began the picture in ten cases, with one cord degeneration. There were fourteen cases beginning with tingling, numbness and stiffness, in which all but two developed cord degeneration. Eighty per cent of the cases having paresthesias as the initial complaint developed cord degeneration, while only 20 per cent of those developing paresthesias during the course of the disease had cord degeneration.

It is seen that the most frequent symptom at the onset is generalized weakness. The high percentage of patients developing cord changes whose initial complaint was neurologic is quite striking. That this is not coincidental is borne out by the figures given by MacBride and Carmichael from a neurologic hospital in London. They found that 78 per cent of their patients with combined cord degeneration of pernicious anemia had neurologic complaints at the onset. Patients who state that their first symptom was tingling are more likely to develop posterolateral sclerosis, while if the tingling develops during the course of the anemia they are less likely to suffer from cord changes. The tingling of the latter group, I believe, is due to peripheral nerve changes and is a result of anemia, and is not restricted to any one type of anemia.

I attempted to determine if the blood count had any relation to the pathologic condition of the cord and in those cases with the full blown neurologic picture the red blood cell count was found to vary from 200,000 to 4,500,000. The lack of red cells is apparently not directly related to the cord changes.

It is well to consider what information neuropathology has to offer. Originally it was thought that there was a definite and specific localization of the pathologic condition in the posterior and lateral columns. Later investigations revealed that not only were both columns not always involved, but that the posterior or lateral may predominate in intensity, resulting in a variation of the clinical picture, and that other tracts also, such as the spinocerebellar tracts, are affected. Lesions of almost complete transverse nature have been reported. The essential pathologic condition consists of small patches of degeneration of the fibers involved. The posterior and lateral columns are often found completely degen-

erated because they are the longest in the cord and there is more chance for the resulting secondary degeneration to be summed up. The lesions consist of degenerative changes in the myelin sheaths, later axis cylinder destruction; all are accompanied by proliferation of the glial elements, which serves to remove the débris. There are never evidences of an inflammatory process. The picture has no specific characteristics and differs in no way from degeneration resulting from any toxic cause. By intrathecal stovaine injections Spielmeyer [28] showed that with smaller doses the posterior columns were most susceptible to changes.

If the combined cord degeneration is produced by the action of a nonspecific toxin, it should be found associated with other diseases which give rise to toxins. The literature contains quite a few such cases but with relatively few necropsies. In some the accuracy of the blood examination may be questioned. Oppenheim [22] and Clarke [29] have seen cord degeneration on an arteriosclerotic basis; Clarke and Nonne as a result of severe secondary anemia; Schultze, Hirschfeld and Nonne report leukemic cases; Hennenberg and Oppenheim, malaria. Zadek, Redlich and Homén report ergot poisoning with the typical cord changes. Lubarsh has had a case with carcinoma and Williamson with diabetes. Marie and Zadek have noted the disease with pellagra and Mayer with lathyrism. Oppenheim has seen cases with lead, arsenic and phosphorus poisoning. Fleiner had a case with Addison's disease, and Sanders with senility. Putnam described the disease first in this country as a result of chronic ill health in women.

Hurst believes that in carcinoma of the stomach the anacidity is the main factor, and states that in the cachetic cases pernicious anemia was probably undiagnosed or that the anemia developed shortly before death.

In order to get some definite data on this subject, I have compiled cases of combined cord degeneration not associated with pernicious anemia. In three cases with the typical neurologic picture there was no anemia, but no other demonstrable etiologic factor was found; therefore, I do no more than mention them. In the following cases not only was there no Addison's anemia, but another cause was definitely proved.

Case 7.—A man, aged 62, complained of dribbling of urine and pains in the legs for a year. He had ataxia and gave a positive Romberg sign. The patellar and ankle jerks were exaggerated. The red blood cells totaled 4,000,000, hemoglobin 75 per cent, blood pressure 170 systolic, 120 diastolic. Necropsy revealed combined cord degeneration and arteriosclerosis with involvement of the vertebral vessels. The bone marrow was normal.

Case 8.—A man, aged 53, complained of abdominal pain and diarrhea. A gastro-intestinal examination was entirely negative. The deep and position senses were lost in the legs. There were ankle clonus and exaggerated reflexes. The

28. Spielmeyer: Neurol. Centralbl. **69,** 1909.
29. Clarke: Brain **27**:29, 1904.

red blood cells totaled 800,000, hemoglobin 30 per cent. The diagnosis was pernicious anemia with combined cord degeneration. Necropsy revealed carcinoma of the colon; the bone marrow was normal.

CASE 9.—A man, aged 55, complained of weakness of the legs for three months. The hands and arms had little power. The skin generally was bronzed. The sensation of pain and the deep and position senses were lost in the legs. The legs were spastic with a bilateral Babinski reflex. The patient was found dead in bed one morning. Necropsy revealed tuberculosis of the suprarenals with combined cord degeneration.

CASE 10.—A woman, aged 37, was unable to walk for eight weeks. She had severe diarrhea and definite mental changes. The skin showed typical pellagra skin lesions. The joint and tendon sense was absent. The ankle jerks were gone; she was ataxic and a Babinski reflex was present on one side. A definite history of dietary imbalance was obtained. She improved with a proper diet.

CASE 11.—A man, aged 63, complained of incontinence. He was ataxic in the lower extremities, had increased deep reflexes, and absent tactile sensation in the legs. The blood and spinal fluid Wassermann reactions were negative. The red blood cells totaled 4,800,000, hemoglobin 80 per cent. A chest examination revealed a chronic diffuse tuberculosis.

CONCLUSIONS

1. Normal gastric acidity may be present in pernicious anemia.

2. The rarity of achylia preceding the anemia by many years makes it improbable that achylia is a predisposing cause. The fact that the anemia may go unrecognized for some time may account for these cases.

3. There is no evidence that there is an intestinal infection in pernicious anemia or that streptococci lying latent in the bowels of these patients are the producers of absorbable toxin.

4. Thirty per cent of pernicious anemia patients develop definite signs of combined cord degeneration.

5. Combined cord degeneration may be caused by the hypothetic toxins producing the pernicious anemia or developing during the course of the disease, but may also be the result of numerous other toxic conditions, such as Addison's disease, carcinoma of the bowel, pellagra and arteriosclerosis.

6. Eighty per cent of patients having paresthesia as the initial complaint developed cord degeneration, while only 20 per cent developed cord degeneration when paresthesia appeared during the course of the disease.

THE EFFECT OF ATROPINE ON GASTRIC FUNCTION IN MAN

A QUANTITATIVE STUDY *

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The general fact that atropine may diminish gastric secretion is familiar to all physicians. In the case of animals, accurate observations are on record, but in spite of the extensive use of the drug in the clinic, no exact information is available as to the details of its action in man. The method that we have recently described [1] for estimating simultaneously the quantity of gastric secretion and discharge lends itself well to the study of this problem and this article deals with the alterations in gastric activity produced in man by administration of atropine. The study is essentially a pharmacologic one, and no attempt will be made to judge the therapeutic value of the drug in clinical disorders of the stomach.

LITERATURE

Keeton, Koch and Luckhardt [2] studied the action of atropine in dogs provided with Pawlow pouches. It was found that large doses of the drug abolished the secretion resulting from food stimulation. The quantity of the secretion and the pepsin concentration were diminished before there was any great alteration in the concentration of acid; this was shown best with relatively small doses of atropine. Injections of gastrin and histamine, on the other hand, if large enough, were followed by reappearance of considerable secretion even after complete temporary inhibition by atropine.

On the clinical side the literature deals largely with special pleading for or against the use of atropine in gastric ulcer, hypersecretion, pylorospasm and other conditions, and one finds few detailed studies of the objective effects of the drug. Riegel,[3] a good many years ago, showed

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* From the medical clinic of the Johns Hopkins University and Hospital.

1. Bloomfield, A. L., and Keefer, C. S.: A Method for the Continuous Estimation of Gastric Secretion and Discharge in Man, Arch. Int. Med. **37**:819 (June) 1926. The formula on page 822, of this article appearing in Arch. Int. Med. **37**:819 (June) 1926, should be $[(\frac{x}{y}) \times A] - A =$ maximum possible amount of juice secreted in ten minute period instead of $[(\frac{y}{x}) \times A] - A =$ maximum possible amount of juice excreted in ten minute period.

2. Keeton, R. W.; Koch, F. C., and Luckhardt, A. B.: Gastrin Studies: II, Response of Stomach Mucosa to Food and Gastrin Bodies as Influenced by Atropine, Am. J. Physiol. **51**:469 (April) 1920.

3. Riegel, F.: Ueber medicamentöse Beeinflussung der Magensaftsecretion, Ztschr. f. klin. Med. **37**:381, 1899.

that following a meal of 1 liter of milk, the amount of stomach contents recovered and the acidity were less if the patient had previously received a dose of atropine. More recently, Bennett [4] and Roberts,[5] using the fractional gruel meal, report the same general results, although only a few cases were studied and in some of them the decrease in acidity was not marked. Crohn,[6] on the other hand, obtained some contradictory results. In two patients with presumably normal secretion, administration of 1 mg. (one-sixtieth grain) of atropine hypodermically was not followed by any demonstrable diminution of acidity when tested with the fractional gruel meal; later, one of these patients was well atropinized by mouth also without effect. In some patients with so-called hypersecretion, on the other hand, the secretion seemed to be checked to some extent although the degree of acidity was unchanged. The results as regards motility were uncertain. Finally, Lockwood and Chamberlin [7] did the usual fractional analysis following an Ewald test meal before and after atropine. They conclude that both motor and secretory activity is depressed but add nothing essentially new to the observations of previous workers. In general the impression seems to prevail that atropine may lessen the normal tonus of the stomach and may abolish abnormal contractions and "pylorospasm." In view of the complexity of the gastric motor mechanism, the data available are not convincing. Bastedo [8] concludes that in the doses usually employed, atropine is wholly without effect on the motor and secretory function of the stomach.

METHODS

The procedure employed in the present work consisted of studying the response of the stomach to a standard stimulus before and after the administration of atropine. As a rule a single hypodermic injection of 2 mg. (one-thirtieth grain) was given; this dose was usually sufficient to produce distinct minor toxic symptoms—tachycardia, dryness of the mouth, blurring of vision, and unpleasant sensations of fulness in the head. The subjects were ward patients, for the most part without digestive symptoms. The test stimulus of 50 cc. of 7 per cent alcohol solution was employed exactly as described in the previous article.[1]

4. Bennett, T. I.: Effect of Belladonna in Hyperchlorhydria, Guy's Hosp. Rep. **71**:54, 1921.

5. Roberts, R. D.: Effect of Belladonna in Hyperchlorhydria, Guy's Hosp. Rep. **71**:446 (Oct.) 1921.

6. Crohn, B. B.: Studies in Fractional Estimation of Gastric Contents: II, Effects of Antacid Medication on Gastric Acidity and Secretion, Am. J. M. Sc. **155**:801 (June) 1918.

7. Lockwood, B. C., and Chamberlin, H. G.: Effect of Atropine on Gastric Function, as Measured by Fractional Analysis, Arch. Int. Med. **30**:806 (Dec.) 1922.

8. Bastedo, W. A.: Points in Pharmacology of Certain Drugs Used for Stomach Effects, Am. J. M. Sc. **159**:53 (Jan.) 1920.

RESULTS

CASE 1.—A. J., a man, aged 56, who entered the hospital for a minor complaint, had marked evidence of vagotonia. There was a bradycardia (pulse rate about 50 per minute) and as the control study of gastric function shows (table 1 and chart 1) he secreted large amounts of gastric juice of high acidity. When the stomach was aspirated it was noted that there were periods of excessive tonus. No essential change in the type of response was noted after the patient had taken 90 drops of tincture of belladonna for five days, except that the volume curve was markedly altered. Variations of this sort are, however, found in successive control examinations of the same person.

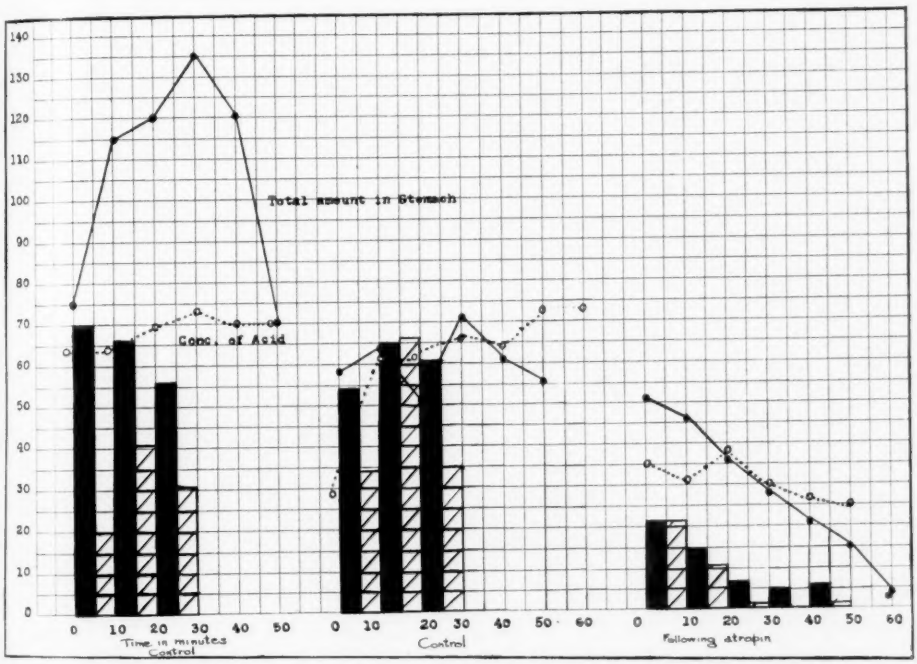

Chart 1.—Observations in case 1. Solid columns indicate secretion and light columns indicate discharge (cc.). The total amount in the stomach is expressed in cc. and the concentration of acid in cubic centimeters of tenth normal hydrochloric acid.

After one-twentieth grain (3 mg.) of atropine there was a great reduction in volume of juice secreted. In fact after the first two ten minute periods, there was almost complete cessation. The acidity of the stomach contents was reduced but less markedly than the volume. The volume curve was strikingly altered. There was a steady fall and the stomach was empty in sixty minutes, but the amount of juice discharged was much less than before atropine administration.

CASE 2.—W. W., a man, aged 53, had pyloric ulcer, with partial pyloric obstruction. The control examination (table 2, chart 2) showed secretion of large amounts of juice and correspondingly great discharge of fluid so that the volume of the stomach contents remained nearly constant. The patency of the pylorus was proved by regurgitation of bile. After 1/30 grain (2 mg.) of

TABLE 1.—*Case 1*

Time of Observation		Total Stomach Contents, Cc.	p_H	Titratable Acid: Dimethyl-phenolphthalein		Volume of Juice Secreted in 10 Minute Period	Volume Discharged in 10 Minute Period	Titratable Acidity of Pure Juice	Remarks
Without Atropin—November 25									
Immediately after test meal		75	1.7	18	22	..	..	64	
10 minutes after test meal		115	1.3	40	46	70	20	65	
20 minutes after test meal		125	1.15	52	58	66	41	70	
30 minutes after test meal		135	1.1	64	66	56	31	74	
40 minutes after test meal		120	1.1	64	70	..	..	71	
50 minutes after test meal		70	1.1	64	70	..	..	70	
After Tincture of Belladonna, 2 cc. Three Times a Day for 5 Days—December 1									
Immediately after test meal		58	1.9	10	14	..	..	..	Pulse rate, 48
10 minutes after test meal		64	1.2	44	50	53	33	62	
20 minutes after test meal		52	1.1	62	68	65	67	62	Pulse rate, 48
30 minutes after test meal		72	1.0	65	71	61	35	73	Pulse rate, 52
40 minutes after test meal		62	1.0	65	61	..	..	70	
50 minutes after test meal		56	1.0	70	78	..	..	78	
After Atropine 1/20 grain (3 mg.)—December 1									
Immediately after test meal	25 minutes after injection of atropine	52	2.9	2	4	..	..	..	Pulse rate, 84
10 minutes after test meal	35 minutes after injection of atropine	46	1.9	12	14	21.5	21.5	32	Pulse rate, 88
20 minutes after test meal	45 minutes after injection of atropine	36	1.7	20	24	15.0	11.0	37	Pulse rate, 88; blurring of vision
30 minutes after test meal	55 minutes after injection of atropine	30	1.7	20	22	7.5	3.5	30	Pulse rate, 88
40 minutes after test meal	65 minutes after injection of atropine	25	1.7	20	22	5.0	0.0	27	Pulse rate, 84
50 minutes after test meal	75 minutes after injection of atropine	15	1.8	20	22	6.0	1.0	25	Pulse rate, 84
60 minutes after test meal	85 minutes after injection of atropine	4	1.9	20	22	..	..	..	

atropine there were no marked toxic symptoms, although the pulse rose moderately. It may be seen, however, that the volume of juice secreted was greatly reduced, 46 cc. in thirty minutes as against 168 cc., whereas the degree of acidity was only slightly depressed. It is of special interest that the volume curve of stomach contents is almost identical before and after atropine although in the latter case the amount of discharge was tremendously reduced—6 cc. in thirty minutes as against 136 cc.

CASE 3.—W. S., a man, aged 23, normal, with no digestive symptoms, had two control examinations (table 3 and chart 3) which showed essentially similar findings: secretion of abundant gastric juice of rather high acidity, with steady, fairly rapid emptying of the stomach. After atropine there was a prompt secretion of juice which was as abundant during the first ten minute period as before atropine. The secretion then rapidly diminishes and after forty minutes

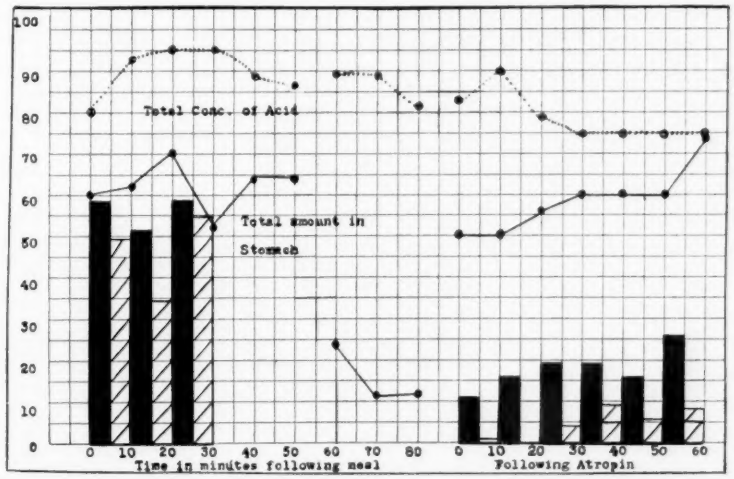

Chart 2.—Observations in case 2.

ceases. The acidity after atropine is much reduced even with active secretion during first period; later it is still further diminished. There is no striking change in motility.

CASE 4.—W. L., a man, aged 22, had a small cyst of the lung (echinococcus?), but was clinically well and had no digestive symptoms. The control examination (table 4 and chart 4) showed that this patient secreted rather large amounts of gastric juice of very low acidity. After atropine the pulse rate was doubled. There was a prompt response to the stomach stimulus and in the first two ten minute periods nearly as much juice was secreted as before atropine; then there was a marked decrease. The acidity of the stomach contents was practically unaffected, although it was probable that the juice secreted in small amounts toward the end of the experiment was of very low acidity. After atropine little juice passed the pylorus and the stomach emptied gradually.

CASE 5.—R. M., a man, aged 40, had attacks of migraine with nausea and vomiting. A control examination (table 5 and chart 5) showed steady secretion of large amounts of juice of relatively low acidity. There was a steady fall in acidity as the test progressed. After atropine the secretion was markedly and uniformly decreased. The acidity also was much diminished. The stomach emptied more quickly but much less fluid passed the pylorus.

TABLE 2.—*Case 2*

Time of Observation		Total Stomach Contents, Cc.	p_H	Titratable Acid: Dimethyl-phenolphthalein		Volume of Juice Secreted in 10 Minute Period	Volume Discharged in 10 Minute Period	Titratable Acidity of Pure Juice	Remarks
Without Atropine—November 23									
Immediately after test meal		60	1.65	20	24	..	..	80	
10 minutes after test meal		62	1.10	64	68	59	47	93	
20 minutes after test meal		70	1.10	80	84	52	34	95	
30 minutes after test meal		52	1.05	84	90	57	55	95	
40 minutes after test meal		64	1.15	78	86	..	..	88	
50 minutes after test meal		64	1.15	82	86	..	..	86	Pulse rate, 68
60 minutes after test meal		..	1.15	88	90	..	..	90	Pulse rate, 68; slight regurgitation of bile
After Atropin, 1/30 grain (2 mg.)—November 23									
Immediately after test meal	35 minutes after atropine	50	2.30	2	4	..	..	..	
10 minutes after test meal	45 minutes after atropine	50	1.65	32	40	12	2	90	Pulse rate, 84
20 minutes after test meal	55 minutes after atropine	56	1.50	40	46	16	0	77	Pulse rate, 72
30 minutes after test meal	65 minutes after atropine	60	1.4	50	54	18	4	75	Pulse rate, 72
40 minutes after test meal	75 minutes after atropine	60	1.3	56	60	19	9	75	Pulse rate, 78
50 minutes after test meal	85 minutes after atropine	60	1.3	60	64	16	6	75	Pulse rate, 80
60 minutes after test meal	95 minutes after atropine	68	1.3	66	70	26	8	75	

CASE 6.—G. M., a man, aged 23, who had chronic nephritis (early), had never had any gastro-intestinal symptoms. The results of examination are shown in table 6 and chart 6. It is seen that before atropine rather large amounts of juice were secreted and discharged so that the stomach was practically empty in forty minutes. After atropine, the stimulus was followed by a prompt secretion which

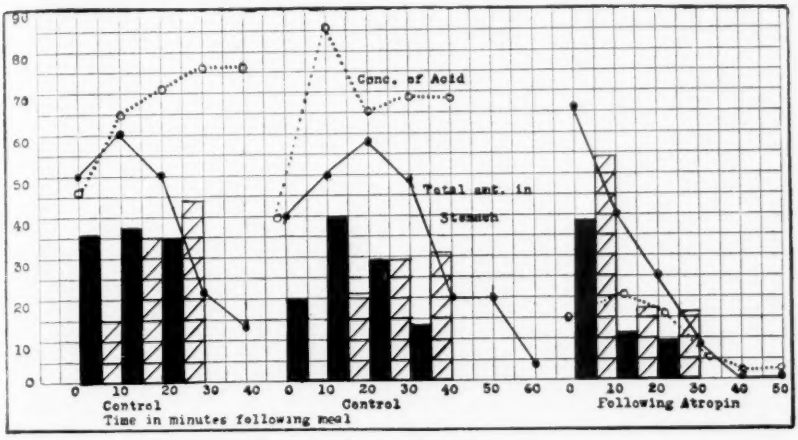

Chart 3.—Observations in case 3.

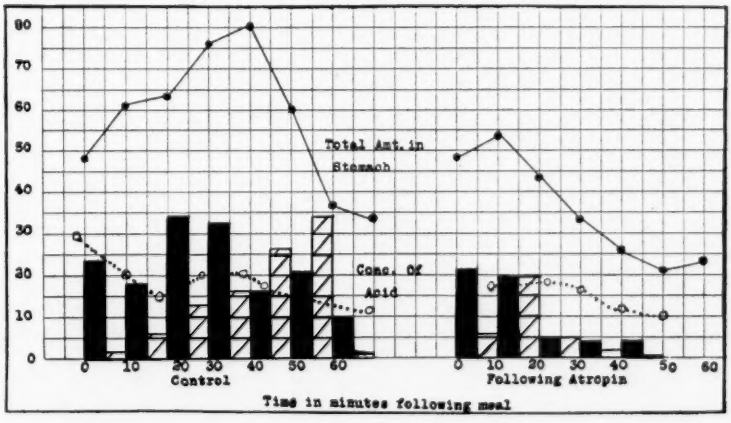

Chart 4.—Observations in case 4.

was, however, not sustained, and after the first ten minute period practically no juice was secreted. The stomach was empty at the same time after atropine as before, but the amount of juice passing the pylorus was very much less—26 cc. in thirty minutes as against 75 cc. The curve of acidity was high and uniform before atropine; after the drug the curve was low and the abrupt fall indicates that as the secretion of juice diminished the acidity fell practically to zero.

TABLE 3.—*Case 3*

Time of Observation		Total Stomach Contents, Cc.	p_H	Titratable Acid: Dimethyl-phenolphthalein	Titratable Acid: Total	Volume of Juice Secreted in 10 Minute Period	Volume Discharged in 10 Minute Period	Titratable Acidity of Pure Juice	Remarks
Without Atropine—November 12									
Immediately after test meal		50	1.9	10	14	..	..	..	
10 minutes after test meal		60	1.4	40	42	35.5	15	65	
20 minutes after test meal		50	1.2	52	60	37.5	35	71	
30 minutes after test meal		22	1.15	62	72	35.0	45	76	
40 minutes after test meal		14	1.15	62	74	..	..	76	
Without Atropine—December 1									
Immediately after test meal		40	2.1	4	6	..	..	..	
10 minutes after test meal		50	1.3	38	42	20	0	85	Pulse rate, 80
20 minutes after test meal		58	1.2	48	52	40	22	65	Pulse rate, 80
30 minutes after test meal		48	1.2	56	60	27	27	68	Pulse rate, 80
40 minutes after test meal		20	1.2	58	62	13	31	68	
50 minutes after test meal		20	1.65	30	..	..	..	..	Stomach contents slightly bile stained and contained much mucus
After Atropine, 1/80 grain (2 mg.)—December 1									
Immediately after test meal	30 minutes after atropine	66	...	4	6	..	..	..	Pulse rate, 128; felt sleepy; arms weak
10 minutes after test meal	40 minutes after atropine	40	3.1	2	14	38	54	20	Pulse rate, 144
20 minutes after test meal	50 minutes after atropine	25	3.0	4	14	12	17	17	Pulse rate, 140
30 minutes after test meal	60 minutes after atropine	8	3.0	0	6	9.5	16.5	6	Pulse rate, 140; things looked smoky
40 minutes after test meal	70 minutes after atropine	1—	3.4	0	..	..	..	1—	Throat very dry
50 minutes after test meal	80 minutes after atropine	1—	4.2	0	..	..	..	1—	Pulse rate, 140

TABLE 4.—*Case 4*

Time of Observation		Total Stomach Contents, Cc.	p_H	Titratable Acid: Dimethyl-phenolphthalein	Titratable Acid: Total	Volume of Juice Secreted in 10 Minute Period	Volume Discharged in 10 Minute Period	Titratable Acidity of Pure Juice	Remarks
Without Atropine—December 8									
Immediately after test meal		48	...	2	6	....	....	..	
10 minutes after test meal		62	...	6	10	23.5	1.5	20	
20 minutes after test meal		64	2.3	6	10	17.5	5.5	15	
30 minutes after test meal		76	2.2	8	16	34.5	12.5	20	Pulse rate, 60
40 minutes after test meal		80	2.2	8	18	32.5	16.5	20	Pulse rate, 64
50 minutes after test meal		60	2.1	10	14	16.5	26.5	15	Pulse rate, 60
60 minutes after test meal		36	2.0	10	14	20.5	31.0	15	Pulse rate, 64
After Atropine, 1/80 grain (2 mg.)—December 8									
Immediately after test meal	25 minutes after atropine	48	...	..	..	..	..	..	
10 minutes after test meal	35 minutes after atropine	54	2.25	6	8	22	6	17	Pulse rate, 124
20 minutes after test meal	45 minutes after atropine	44	2.2	6	12	19	19	19	Pulse rate, 132
30 minutes after test meal	55 minutes after atropine	34	2.2	6	12	5	5	17	Pulse rate, 124
40 minutes after test meal	65 minutes after atropine	26	2.2	6	12	4	2	16	Pulse rate, 112
50 minutes after test meal	75 minutes after atropine	22	2.2	6	8	4	0	10	Pulse rate, 112
60 minutes after test meal	85 minutes after atropine	24	...	0	..	..	..	..	Pulse rate, 112

CASE 7.—D. W., a man, aged 40, with hypertension (slight), had no gastric symptoms. The control test (table 7 and chart 7) showed a prompt secretion of rather large amounts of juice of high acidity. The volume of juice then steadily decreased and toward the end of the test there was a marked fall in acidity as

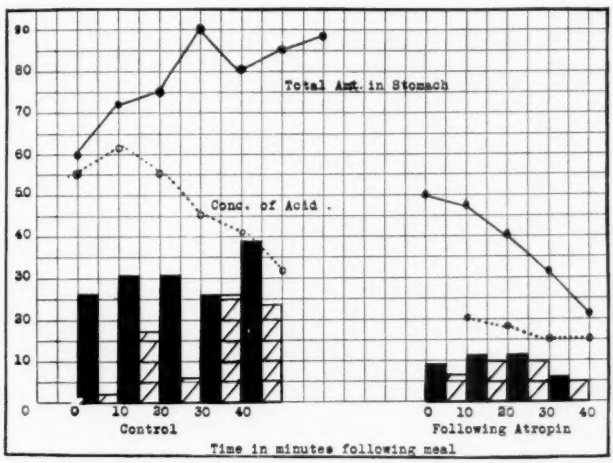

Chart 5.—Observations in case 6.

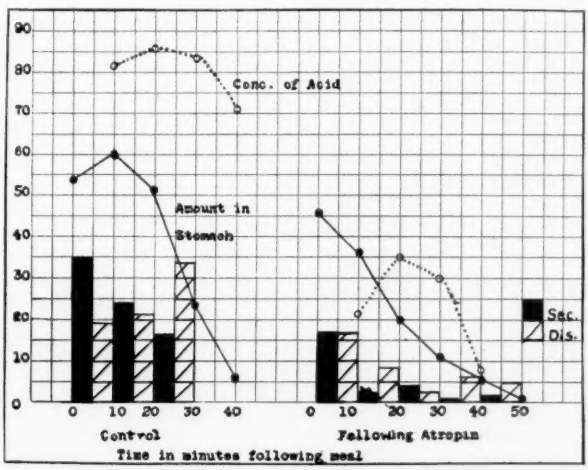

Chart 6.—Observations in case 6.

well. After atropine there was a brisk temporary response followed by secretion of only small quantities of juice. The same marked fall in acidity as before atropine was seen toward the end of the test. There was no striking alteration in motility.

TABLE 5.—*Case 5*

Time of Observation		Total Stomach Contents, Cc.	p_H	Titratable Acid: Dimethyl-phenolphthalein		Volume of Juice Secreted in 10 Minute Period	Volume Discharged in 10 Minute Period	Titratable Acidity of Pure Juice	Remarks
Without Atropine—November 18									
Immediately after test meal		60	1.6	16	20	...	....	..	
10 minutes after test meal		72	1.4	30	36	25.5	3.5	62	
20 minutes after test meal		75	1.4	36	42	30.5	17.5	57	
30 minutes after test meal		90	1.4	34	44	31.0	6.0	55	Pulse rate, 64
40 minutes after test meal		80	1.5	30	40	26.0	26.0	45	Pulse rate, 64
50 minutes after test meal		85	1.6	26	38	38.0	23.0	41	Pulse rate, 64
After Atropine—November 18									
Immediately after test meal	30 minutes after atropine	50	4.4	0	2	..	..	..	Pulse rate, 80
10 minutes after test meal	40 minutes after atropine	48	2.3	4	8	9	7	20	Pulse rate, 76
20 minutes after test meal	50 minutes after atropine	40	2.1	6	10	12	10	18	Pulse rate, 80
30 minutes after test meal	60 minutes after atropine	32	2.1	6	10	12	10	15	Pulse rate, 88
40 minutes after test meal	70 minutes after atropine	22	2.15	6	12	5.5	5	15	

TABLE 6.—*Case 6*

Time of Observation		Total Stomach Contents, Cc.	p_H	Titratable Acid: Dimethyl-phenolphthalein		Volume of Juice Secreted in 10 Minute Period	Volume Discharged in 10 Minute Period	Titratable Acidity of Pure Juice	Remarks
Without Atropine—November 10									
Immediately after test meal		54	1.9	14	16	..	..	..	Pulse rate, 82
10 minutes after test meal		60	1.2	38	46	35	19	82	
20 minutes after test meal		52	1.15	56	62	24	22	86	
30 minutes after test meal		24	1.1	62	70	16	34	85	
40 minutes after test meal		6	1.3	62	70	..	..	..	Pulse rate, 80
After Atropine, 1/30 grain (2 mg.)—November 10									
Immediately after test meal	25 minutes after atropine	46	3.3	0	0	..	..	..	Pulse rate, 90
10 minutes after test meal	35 minutes after atropine	36	2.4	4	8	16	16	22	Pulse rate, 128
20 minutes after test meal	45 minutes after atropine	20	1.9	8	14	2	8	35	
30 minutes after test meal	55 minutes after atropine	12	2.0	14	16	4	2	30	
40 minutes after test meal	65 minutes after atropine	6	2.0	2	4	1	7	6	
50 minutes after test meal	75 minutes after atropine	2	2.1	..	..	2	5	..	No other symptoms of atropine effect

CASE 8.—G. W., a man, aged 49, convalescent from bronchopneumonia, had a normal temperature for several weeks. He had never had any digestive symptoms. The two control examinations (chart 8 and table 8) showed essentially the same results—secretion of a moderate amount of juice of moderate acidity, with steady emptying of the stomach. After the administration of atropine the volume secreted

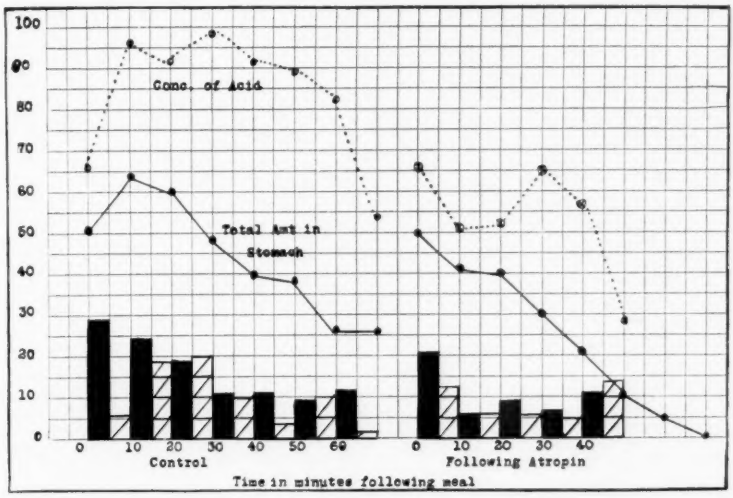

Chart 7.—Observations in case 7.

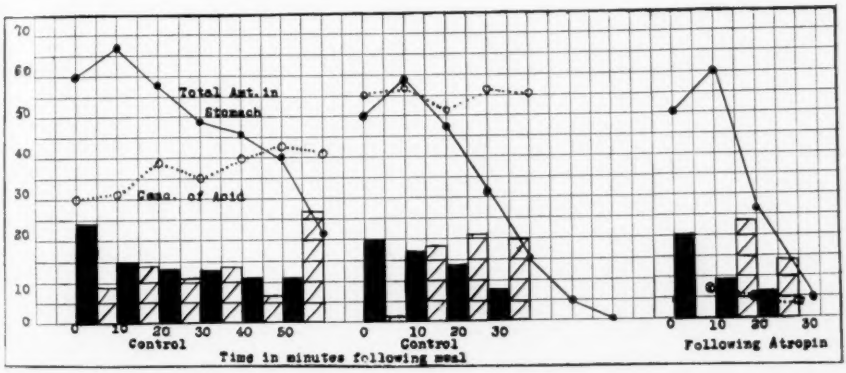

Chart 8.—Observations in case 8.

was somewhat diminished—34.5 cc. in thirty minutes as against 52 cc. and 53 cc., but the degree of acidity was tremendously reduced, free acid as measured with dimethyl being entirely abolished. The stomach was empty sooner after atropine than before, but the amount of juice discharged was much less—17 cc. in thirty minutes as against 42 cc. and 36 cc.

TABLE 7.—*Case 7*

Time of Observation		Total Stomach Contents, Cc.	p_H	Titratable Acid: Dimethyl-phenolphthalein		Volume of Juice Secreted in 10 Minute Period	Volume Discharged in 10 Minute Period	Titratable Acidity of Pure Juice	Remarks
Without Atropine—December 8									
Immediately after test meal		52	1.8	8	10	....	....	..	
10 minutes after test meal		64	1.25	44	48	27.5	5.5	96	
20 minutes after test meal		60	1.20	60	64	24.0	18.0	92	
30 minutes after test meal		48	1.20	72	76	18.0	20.0	98	
40 minutes after test meal		40	1.20	74	78	12.0	10.0	92	
50 minutes after test meal		38	1.20	70	76	11.5	3.5	87	
60 minutes after test meal		26	1.30	72	76	8.0	10.0	83	Pulse rate, 68
70 minutes after test meal		26	1.50	42	52	12.0	2.0	54	Pulse rate, 80
After Atropine, 1/30 grain (2 mg.)—December 11									
Immediately after test meal	50 minutes after atropine	50	1.9	8	10	....	....	..	Pulse rate, 96
10 minutes after test meal	60 minutes after atropine	42	1.6	22	26	21.5	13.5	52	Pulse rate, 96
20 minutes after test meal	70 minutes after atropine	40	1.5	30	32	5.5	5.5	53	Pulse rate, 96
30 minutes after test meal	80 minutes after atropine	30	1.4	42	46	8.0	6.0	65	Pulse rate, 100
40 minutes after test meal	90 minutes after atropine	22	1.4	44	46	7.0	5.0	59	Pulse rate, 100
50 minutes after test meal	100 minutes after atropine	10	1.5	30	32	12.0	14.0	34	Pulse rate, 96
60 minutes after test meal	110 minutes after atropine	5	1.5	..	..	....	....	..	Pulse rate, 80
70 minutes after test meal	120 minutes after atropine	0	...	..	..	....	....	..	Pulse rate, 90

TABLE 8.—*Case 8*

Time of Observation		Total Stomach Contents, Cc.	p_H	Titratable Acid: Dimethyl-phenolphthalein		Volume of Juice Secreted in 10 Minute Period	Volume Discharged in 10 Minute Period	Titratable Acidity of Pure Juice	Remarks
Without Atropine—October 21									
5 minutes after test meal		60	2.1	6	10	....	..	30	
15 minutes after test meal		67	1.95	11	17	24.5	9.5	32	
25 minutes after test meal		58	1.8	18	24	15.7	15	37	
35 minutes after test meal		48	1.7	20	26	13	11	35	
45 minutes after test meal		46	1.65	23	33	13	14	40	
55 minutes after test meal		40	1.6	30	37	11.5	7	43	
65 minutes after test meal		22	1.55	32	38	9	15	42	
Without Atropine—November 10									
Immediately after test meal		50	...	12	14	..	..	..	Pulse rate, 84
10 minutes after test meal		58	1.45	18	22	20	2	55	Pulse rate, 88
20 minutes after test meal		47	1.45	24	34	17.5	18.5	50	Pulse rate, 80
30 minutes after test meal		32	1.4	30	40	14.5	21.5	51	Pulse rate, 84
40 minutes after test meal		15	1.4	34	46	7.5	20.0	56	Pulse rate, 80
50 minutes after test meal		5	1.4	40	50	..	..	55	Pulse rate, 80
After Atropine, 1/40 grain (1.5 mg.)—November 10									
Immediately after test meal	50 minutes after atropine	50	3.4	0	2	..	..	..	Pulse rate, 92; occasional extrasystoles
10 minutes after test meal	60 minutes after atropine	60	3.5	0	2	20	0	8	Pulse rate, 84
20 minutes after test meal	70 minutes after atropine	26	3.4	0	2	9	23	5	Pulse rate, 86
30 minutes after test meal	80 minutes after atropine	5	3.4	0	2	5.5	14.5	4	Pulse rate, 84; no dryness of mouth; no dilatation of pupils

CASE 9.—E. G., a woman, aged 28, who had an old tuberculous peritonitis, was clinically well and had no digestive symptoms. The control examinations (table 9 and chart 9) showed secretion of small amounts of juice of rather high acidity. After atropine the secretion was practically abolished, although there was almost no change in the volume curve of the stomach contents. There was a marked clinical reaction to the atropine.

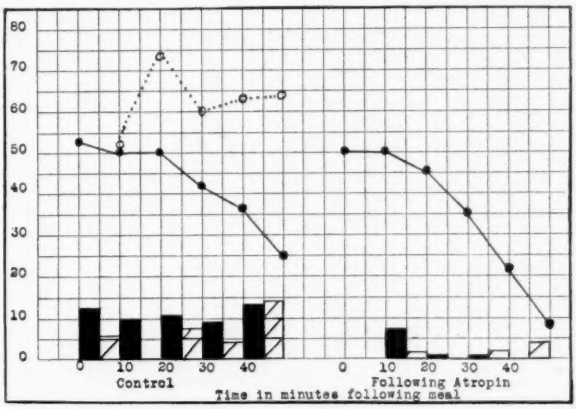

Chart 9.—Observations in case 9.

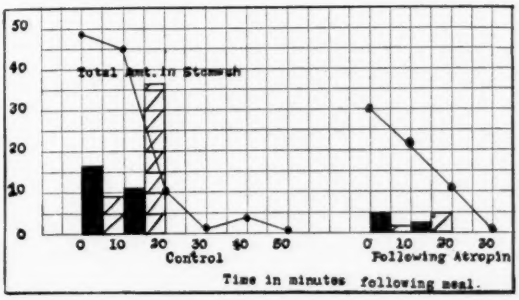

Chart 10.—Observations in case 11.

CASE 10.—C. G., a man, aged 24, was clinically diagnosed as normal. The control examination (table 10) showed very rapid emptying of the stomach. It was only possible to calculate secretion for one period of ten minutes during which 35 cc. of juice was secreted. Two tests done after atropine showed marked differences in motility. In the second test it was seen that after a moderate initial response the secretion of juice was practically abolished. There was marked clinical atropine effect on both occasions.

CASE 11.—S. M., a man, aged 50, had pernicious anemia. Hemoglobin was 32 per cent. No digestive symptoms were present. The results of examination before and after atropine are shown in table 11. The volume of secretion, already

TABLE 9—*Case 9*

Time of Observation	Total Stomach Contents, Cc.	p_H	Titratable Acid: Dimethyl-phenolphthalein		Volume of Juice Secreted in 10 Minute Period	Volume Discharged in 10 Minute Period	Titratable Acidity of Pure Juice	Remarks
Without Atropine—December 7								
Immediately after test meal	53	2.2	6	8	....	...	..	
10 minutes after test meal	50	1.8	16	18	12.5	5.5	50	
20 minutes after test meal	50	1.6	32	36	10.0	0.0	73	Pulse rate, 92
30 minutes after test meal	42	1.5	30	36	10.5	7.5	60	Pulse rate, 96
40 minutes after test meal	36	1.4	36	44	8.0	4.0	63	
50 minutes after test meal	25	1.5	40	46	13.0	14.0	64	
After Atropine, 1/30 grain (2 mg.)—December 7								
Immediately after test meal	50	3.2	0	4	...	...	..	
10 minutes after test meal	50	3.2	0	4	?	...	..	Pulse rate, 152; palpitation
20 minutes after test meal	45	3.2	0	4	7.0	2.0	..	Pulse rate, 156
30 minutes after test meal	35	3.4	0	4	0.5	0.0	..	Pulse rate, 144
40 minutes after test meal	23	3.6	0	4	0.5	1.5	..	Pulse rate, 156
50 minutes after test meal	9	4.0	0	6	0.0	4.0	..	Pulse rate, 144; slight nausea

TABLE 10.—*Case 10*

Time of Observation		Total Stomach Contents, Cc.	p_H	Titratable Acid: Dimethyl-phenolphthalein		Volume of Juice Secreted in 10 Minute Period	Volume Discharged in 10 Minute Period	Titratable Acidity of Pure Juice	Remarks
Without Atropine—November 14									
Immediately after test meal		40	...	6	10	..	..	..	
10 minutes after test meal		25	1.6	30	38	35	40	49	
20 minutes after test meal		12	...	26	34	..	..	..	Pulse rate, 84
After Atropine, 1/30 grain (2 mg.)—November 14									
Immediately after test meal	20 minutes after atropine	25	...	10	14	..	..	..	Pulse rate, 136
10 minutes after test meal	30 minutes after atropine	15	2.2	4	12	?	?	..	Pulse rate, 140
20 minutes after test meal	40 minutes after atropine	0	...	..	..	?	?	..	Pulse rate, 150; mouth dry; palpitation; cannot read
30 minutes after test meal	50 minutes after atropine	0.5	4.2	..	..	..	..	..	Pulse rate, 130
After Atropine, 1/30 grain (2 mg.)—November 20									
Immediately after test meal	25 minutes after atropine	50	5.2	0	..	..	..	..	Pulse rate, 132
10 minutes after test meal	35 minutes after atropine	43	2.4	2	6	14	21	13	Pulse rate, 132
20 minutes after test meal	45 minutes after atropine	22	2.4	2	6	18	15	18	Pulse rate, 132
30 minutes after test meal	55 minutes after atropine	20	2.3	4	8	4	4	10	Pulse rate, 136; nausea; headache; palpitation; cannot read
40 minutes after test meal	65 minutes after atropine	15	2.8	1	3	6	1	3	Pulse rate, 132
50 minutes after test meal	75 minutes after atropine	8	3.0	0	2	1	1	3	Pulse rate, 124

scant, was still further diminished and at the end of thirty minutes had apparently ceased. The drop in p_H from 7.2 to 6.6 does not indicate secretion of a more acid juice after atropine; the alkaline mucus of the stomach had been washed out and p_H 6.6 simply represents the p_H of the test meal.

CASE 12.—A. M., a woman, aged 29, with stricture of the rectum and syphilis, had never had any gastric symptoms. This patient had no free hydrochloric acid (table 12) although the moderate amounts of juice which she secreted possessed some acidity as evidenced by the fall in the p_H of the stomach contents from 7.2 to 5.0. After atropine the secretion, already scant, was further reduced and eventually practically abolished, although it still contained some acid. There was no striking alteration in motility.

COMMENT

A survey of the foregoing protocols shows several striking facts:

1. The effect of atropine on the volume of gastric juice. In a general way it is immediately apparent that the amount of secretion is smaller after atropine than in persons not under the influence of the

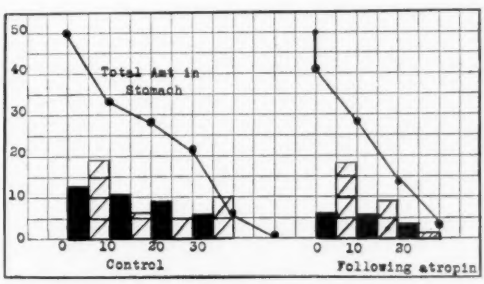

Chart 11.—Observations in case 12.

drug. There are several points about the type of reaction, however, which require special comment. In the control examinations secretion begins promptly after the introduction of the stimulus and usually is maintained at a steady level or gradually diminishes. After atropine on the other hand, in many of the cases there was a prompt response that lasted only during the first ten minute period and was then followed by a marked diminution or even cessation of secretion. In other words, not only was the total amount of secretion diminished, but the type of secretion curve was markedly altered (cases 1, 3, 4, 6, 7, 8, 9 and 10). It is of interest also that the patients were well under the influence of atropine as evidenced by the clinical reaction at the moment when the test stimulus was introduced. Repeated aspiration showed that at this time the fasting secretion in most of the cases had ceased. In spite of this inhibition the test stimulus was still able to evoke secretion which in some cases (cases 3, 4, 7 and 8) was nearly as abundant during the

TABLE 11.—*Case 11*

Time of Observation		Total Stomach Contents, Cc.	p_H	Titratable Acid: Dimethyl-phenolphthalein		Volume of Juice Secreted in 10 Minute Period	Volume Discharged in 10 Minute Period	Titratable Acidity of Pure Juice	Remarks
Without Atropine—December 1									
Immediately after test meal		48	...	0	..	..	..	..	
10 minutes after test meal		45	7.2	0	..	16.0	8.0	..	Pulse rate, 88
20 minutes after test meal		10	7.2	0	..	10.5	35.5	..	
30 minutes after test meal		1	7.2	0	..	..	..	..	
After Atropine, 1/30 grain (2 mg.)—December 1									
Immediately after test meal	35 minutes after atropine	30	...	0	..	..	..	..	
10 minutes after test meal	45 minutes after atropine	23	6.6	0	..	5	2	..	Pulse rate, 100
20 minutes after test meal	55 minutes after atropine	11	6.6	0	..	3	5	..	Pulse rate, 100
30 minutes after test meal	65 minutes after atropine	0	...	0	..	..	..	..	Pulse rate, 100

TABLE 12.—*Case 12*

Time of Observation		Total Stomach Contents, Cc.	p_H	Titratable Acid: Dimethyl-phenolphthalein		Volume of Juice Secreted in 10 Minute Period	Volume Discharged in 10 Minute Period	Titratable Acidity of Pure Juice	Remarks
Without Atropine—December 2									
Immediately after test meal		50	7.2	0	2	..	..	..	
10 minutes after test meal		34	7.0	0	4	13	19	..	Pulse rate, 88
20 minutes after test meal		28	7.0	0	..	11	7	..	Pulse rate, 88
30 minutes after test meal		22	6.2	0	..	9	5	..	
40 minutes after test meal		6	5.0	0	..	6	10	..	
After Atropine, 1/30 grain (2 mg.)—December 7									
Immediately after test meal	25 minutes after atropine	42	7.0	0	..	..	..	..	Pulse rate, 128
Immediately after test meal	35 minutes after atropine	27	7.0	0	..	5.5	18.5	..	Pulse rate, 136
Immediately after test meal	45 minutes after atropine	14	5.0	0	..	5.5	8.5	..	Pulse rate, 128
Immediately after test meal	55 minutes after atropine	4	5.2	0	..	3.5	1.5	..	Pulse rate, 120

first ten minute period as in the control examinations without atropine. These facts are shown quantitatively in table 13.

2. The effect of atropine on the degree of acidity of the gastric juice. Keeton, Koch and Luckhardt pointed out that in dogs the volume of juice diminished after atropine more rapidly than the acidity of the secretion. Under the conditions of our experiments this seems to be true in many instances but is not uniformly apparent. In case 3, for example, secretion was not diminished in the first ten minute period although the acidity was markedly decreased, and in case 9, in which there was no titratable free acid after atropine, a small but definite secretion of juice took place. On the other hand, as the secretion becomes markedly diminished it is clear that the acidity falls to low figures, although we have no data on the actual acidity of the juice as

TABLE 13.—*Comparison of Volume of Secretion and Acidity Before and After Injection of Atropine*

	Volume Secreted in First 10 Minute Period		Total Volume Secreted		Highest Titratable Acidity	
Case	Before Atropine, Cc.	After Atropine, Cc.	Before Atropine, Cc.	After Atropine, Cc.	Before Atropine	After Atropine
1	70	21.5	192 (30 minutes)	36 (30 minutes)	74	37
2	59	12.0	168 (30 minutes)	46 (30 minutes)	95	90
3	35.5	38.0	108 (30 minutes)	59.5 (30 minutes)	76	20
4	23.5	22.0	124.5 (50 minutes)	54 (50 minutes)	20	19
5	25.5	9.0	113 (40 minutes)	38.5 (40 minutes)	62	20
6	35.0	16.0	75 (30 minutes)	22 (30 minutes)	86	35
7	27.5	21.5	93 (50 minutes)	54 (50 minutes)	48	65
8	24.5	20.0	53 (30 minutes)	34.5 (30 minutes)	43	8
9	12.5	?	54 (50 minutes)	8.0 (50 minutes)	73	0
10	35.0	14.0	.....	.....	49	18
11	16.0	5.0	265 (20 minutes)	8.0 (20 minutes)	0	0
12	13.0	5.5	33 (30 minutes)	14.5 (30 minutes)	0	0

secreted but only estimation of the titratable acidity of the stomach contents at various intervals after stimulation.

A summary of the actual quantitative relations is given in table 13.

3. Effect of atropine on motility of the stomach. A survey of the volume curves of stomach contents shows that the stomach almost invariably became empty sooner after atropine than before the drug was given. On the other hand, owing to lessened secretion less fluid passed the pylorus in a given time. Furthermore, there are normally (as will be pointed out in another article) great variations in the speed of emptying of the stomach as tested by this method and these variations are also seen after atropine. The results of repeated tests of motility in the same patients (not shown in the foregoing protocols) are summarized in table 14.

On the whole, then, there is no evidence in these tests that the motility of the stomach was essentially altered. The actual amounts of gastric contents discharged before and after atropine in relation to the emptying time are summarized in table 15.

SUMMARY

1. After doses of atropine large enough to produce outspoken clinical pharmacologic effects, the introduction of 50 cc. of 7 per cent alcohol solution is followed by a secretion of gastric juice.

TABLE 14.—*Emptying Time of Stomach on Successive Occasions After Injection of Atropine, One-Thirtieth Grain (Test Meal, 50 cc. of 7 Per Cent Alcohol Solution)*

Case	Emptying Time (Minutes) First Test	Emptying Time (Minutes) Second Test	Emptying Time (Minutes) Third Test	Emptying Time (Minutes) Fourth Test
122	20	30	..	..
126	5	20	20	50
138	5	20	..	..
140	20	60	..	..

TABLE 15.—*Emptying Time of Stomach and Amount of Gastric Discharge Before and After Atropine*

	Before Atropine		After Atropine	
Case	Emptying Time, Minutes	Amount of Contents Discharged	Emptying Time, Minutes	Amount of Contents Discharged
1	50+ (70 cc. still present)	92 (30 minutes)	60	37 (30 minutes)
2	50+ (64 cc. still present)	136 (30 minutes)	60+ (75 cc. still present)	29 (60 minutes)
3	60	80 (40 minutes)	40	87.5 (30 minutes)
4	70+ (34 cc. still present)	96.5 (70 minutes)	60+ (24 cc. still present)	32 (50 minutes)
5	60+ (88 cc. still present)	76.0 (50 minutes)	40+ (22 cc. still present)	32 (40 minutes)
6	40	75 (30 minutes)	40	38 (50 minutes)
7	70+ (25 cc. still present)	69 (40 minutes)	60	70 (50 minutes
8	50	62 (40 minutes)	30	37.5 (30 minutes)
9	50+ (25 cc. still present)	31 (50 minutes)	50	7.5 (50 minutes)
10	40	41 (40 minutes)	30	28.5 (30 minutes)
12	30	43.5 (30 minutes)	30	7.0 (20 minutes)

2. This secretion takes place even after fasting secretion has been abolished.

3. The curve of secretion is altered as to form after atropine and the total volume of secretion is, as a rule, markedly diminished.

4. The degree of acidity is reduced, but there is no parallel relation between degree of reduction of volume and degree of reduction of acidity.

5. No definite changes in gastric motility can be ascribed to atropine in the present experiments.

THE TREATMENT OF POLYCYTHEMIA VERA (ERYTHREMIA) WITH PHENYLHYDRAZINE *

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INTRODUCTION

The use of phenylhydrazine as a therapeutic agent followed its use experimentally in producing hepatic lesions, when destruction of the erythrocytes was noted. Hoppe-Seyler [1] in 1885 was the first to employ hydrazine experimentally in animals, and in 1908 Morawitz and Pratt [2] used it specifically for the purpose of producing experimental anemia in animals. Eppinger and Kloss [3] in 1918 were the first to apply it clinically in cases of polycythemia vera. They observed a fall in the erythrocytes and hemoglobin, mild jaundice and dark urine. Taschenberg [4] reported details of the treatment of a woman with polycythemia vera. The patient had splenomegaly; the hemoglobin was 140 per cent, and the erythrocytes numbered 8,500,000 for each cubic millimeter. She was given a total of 3 Gm. of phenylhydrazine hydrochloride over a period of thirteen days, and a year later 4.25 Gm. in twenty-one days, with definite effect on the blood and the development of jaundice each time. Levi [5] reported a case of polycythemia vera in which 7.5 Gm. of phenylhydrazine had been given daily over a period of one and one-half years. The patient died from intercurrent disease. Necropsy revealed "raspberry" bone marrow, splenomegaly, coronary sclerosis, pneumonia and cirrhosis of the liver. The possible effect of phenylhydrazine in the production of cirrhosis of the liver is of course of crucial importance. Cirrhosis of the liver has been observed in cases of polycythemia in which no treatment was given, and may be related to overwork of the

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* From the Division of Medicine, Mayo Clinic.

* Read before the American Society for Clinical Investigation, Atlantic City, May 3, 1926.

1. Hoppe-Seyler, G.: Ueber die Wirkung des Phenylhydrazins auf den Organismus, Ztschr. f. physiol. Chem. **9**:34-39, 1884-1885.

2. Morawitz, P., and Pratt, J.: Einige Beobachtungen bei experimentellen Anämien, München. med. Wchnschr. **2**:1817-1819, 1908.

3. Eppinger, H., and Kloss, K.: Zur Therapie der Polyzythämie, Therap. Monatsh. **32**:322-326, 1918.

4. Taschenberg, E. W.: Ueber die Behandlung der Polyzythämie mit Phenylhydrazin, Deutsche med. Wchnschr. **47**:774-775 (July 7) 1921.

5. Levi, Ernst: Ueber die Ursache der Lebercirrhose bein Polycythämie, Ztschr. f. klin. Med. **100**:777-784, 1924.

liver from increase in the amount of blood destroyed. Owen [6] reported five cases of polycythemia vera in which phenylhydrazine had been given over periods of months, with very definite destruction of blood, and the development of mild anemia. He also noted the development of leukocytosis early in the administration of the drug, and suggested that the degree of leukocytosis might serve as an index of the amount of the drug required. He believes that if leukocytosis is marked, it is safer not to give the drug until the leukocyte count is reduced. The therapeutic results were quite satisfactory, and no harmful effects were observed.

COMPOSITION OF PHENYLHYDRAZINE

The formula for phenylhydrazine is $C_6H_5NH.NH_2$. Hoppe-Seyler has shown that in the experimental animal given phenylhydrazine subcutaneously the drug is very toxic, that it destroys red corpuscles by its reducing effect on hemoglobin, and is likewise a powerful protoplasmic poison. Bodansky,[7] while studying the injury to the liver caused by different hydrazine compounds, found marked destruction of the red corpuscles, hyperpigmentation of the spleen, and pigmentation with extensive degeneration of the liver in a dog weighing 5.9 Kg. that had received subcutaneous injections of phenylhydrazine hydrochloride, totaling 360 mg. In another experiment a decrease in the fructose tolerance was manifested after the first dose of 150 mg. of the drug, and in twelve days the erythrocytes decreased from 5,640,000 to 910,000 for each cubic millimeter. This change in the fructose test, before and after phenylhydrazine poisoning was interpreted as evidence of hepatic insufficiency. Bodansky compares the effect of a number of derivatives of hydrazine: acetyl phenylhydrazine, methyl phenylhydrazine, p-hydrazinbenzoic acid, diphenylhydrazine hydrochloride and others. The formula of acetyl phenylhydrazine is $C_6H_5NH.NHCOCH_3$. This was found to have a marked reducing effect on the hemoglobin but not of the same degree as phenylhydrazine. In one experiment on a dog weighing 10.5 Kg. two injections of acetyl phenylhydrazine, totaling 0.71 Gm., were given. The animal became markedly anemic. Very little destructive change could be demonstrated in the hepatic cells.

Underhill and Karelitz [8] studied the carbohydrate metabolism in dogs injected with hydrazine sulphate, and found hypoglycemia and an

6. Owen, Trevor: A Case of Polycythaemie Vera with Special Reference to the Familial Features and Treatment with Phenylhydrazine, Bull. Johns Hopkins Hosp. **35**:258-262 (Aug.) 1924.

7. Bodansky, Meyer: The Action of Hydrazine and Some of Its Derivatives in Producing Liver Injury as Measured by the Effect on Levulose Tolerance, J. Biol. Chem. **58**:799-811 (Jan.) 1924.

8. Underhill, F. P., and Karelitz, Samuel, Jr.: The Influence of Hydrazine upon Blood Concentration and Blood Sugar Content, J. Biol. Chem. **58**:147-151 (Nov.) 1923.

increase in the concentration of the blood. Wells [9] investigated injury to the liver with the hydrazine compounds, and found a typical picture of fatty degeneration of the parenchymatous cells beginning at the center of the lobules and progressing outward. As Owen [10] has said, the importance of these observations lies in the fact that certain of the hydrazine compounds have a greater toxic effect on the liver than others. The substitution of a methyl and acetyl group in the benzol ring, as shown by Bodansky, decreases the hepatic damage while the destructive effect on the blood is still retained. At present we are using acetyl phenylhydrazine experimentally with a view to its later use in man.

It will be noted that experimentally the hydrazine drugs are administered subcutaneously. In one of our experiments 200 mg. for each kilogram of body weight of the dog was given subcutaneously; marked destruction of blood occurred, and the animal died within five days. When the drug is given by mouth, the toxic effects are much less. In its clinical administration we have given the phenylhydrazine hydrochloride in capsules by mouth. The low toxicity of the drug, when given by mouth to human beings, contrasts sharply with its effect on dogs when given subcutaneously.

Experiments in vitro have been carried out on the effect of phenylhydrazine on erythrocytes. No hemolytic effect occurred with varying dilutions of the drug in test tubes. Data on the mode of excretion of the drug are lacking.

METHODS OF STUDY [11]

The total circulating plasma and blood volumes were ascertained by the dye method,[12] congo red being employed. Circulating hemoglobin was estimated by multiplying the grams of hemoglobin per cent by the total circulating blood volume. The acid hematin method was used for determining the hemoglobin; the normal standard of 15.6 Gm. for each 100 cc. of blood was used as 100 per cent. Bromsulphalein was used to study hepatic function. The fructose tolerance test was carried out in three cases. Quantitative determinations of the size and number of capillaries of the skin were made during different periods of the disease.

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9. Wells, H. G.: The Pathological Anatomy of Hydrazine Poisoning, J. Exper. Med. **10**:457-464, 1908.

10. Owen, Trevor: The Treatment of Erythemia with Phenylhydrazine, J. A. M. A. **85**:2027-2032 (Dec. 26) 1925.

11. Brown, G. E., and Giffin, H. Z.: Studies of the Capillaries and Blood Volume in Polycythemia Vera, Am. J. M. Sc. **166**:489-502 (Oct.) 1923; Studies of the Vascular Changes in Cases of Polycythemia Vera, Am. J. M. Sc. **71**:157-168 (Feb.) 1926.

12. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547-576 (Oct.) 1915; also Tr. A. Am. Phys. **30**:102-106, 1915.

STUDIES DURING TREATMENT

The effect of phenylhydrazine hydrochloride in destroying blood is decisive. Its exact mode of action is not known; however, it is known to exert a reducing action on hemoglobin. Hemoglobin is split into its pigment and protein fractions. The destruction of the cells occurs early, an increase of serum bilirubin having been noted after the second dose of the drug, that is, after 0.2 Gm. has been given. The urine becomes progressively darker, keeping pace with the destruction of the blood. In all our cases sufficient amounts of the phenylhydrazine have been given to produce definite anemia. The effect of the drug was discernible for from seven to ten days after it had been discontinued, a further decrease of approximately 1,000,000 cells occurring. We have borne this fact in mind in regulating the dose, lately discontinuing the drug when the erythrocytes became decreased to approximately 4,500,000 for each cubic millimeter. The leukocytes showed the characteristic increase described by others, in one case (case 3) reaching 53,000. The leukocytosis persisted for varying periods, in one case for at least two months. The effect on the blood platelets was followed in three cases. In two the count was normal; in one the platelet count was high at the beginning of treatment and gradually diminished until it was about normal when the patient was dismissed from observation. The change in blood volume was striking. As the drug acts selectively on the erythrocytes, the change in the total blood volume is due largely to a decrease in the circulating cell volume. When a moderate degree of anemia is approached, the plasma volume increases, as has been described by Keith in cases of secondary anemia due to loss of blood. This change, however, is not marked and appears only when there is definite evidence of anemia. There was also a loss in the total amount of circulating hemoglobin of from 1.1 to 3.3 Kg. The serum bilirubin curve rose with a direct relationship to blood destruction. Jaundice usually appeared after 2.5 Gm. of phenylhydrazine hydrochloride had been administered; at this time the serum bilirubin was usually more than 4 mg. for each 100 cc. of blood. The sclerae were definitely stained and the skin in two cases was perceptibly jaundiced.

Study of hepatic function, both before and after the administration of phenylhydrazine hydrochloride, has shown no retention of bromsulphalein.[13] Determinations were made during different stages of destruction of blood. The fructose tolerance test made in three cases was satisfactory. The renal function showed no significant changes. Studies on the protein metabolism of the blood and urine during the period of

13. Greene, C. H., and Conner, H. M.: Diseases of the Liver, V. A Comparative Study of Tests for Hepatic Function in Certain Diseases of the Hematopoietic System, Arch. Int. Med., to be published.

destruction of blood have been carried out in detail. It has been shown that there is a marked increase in the output of urinary nitrogen during the period of blood destruction; accompanying increases were demonstrated in the blood urea. These findings will be discussed in detail by Huffman.[14] Electrocardiographic studies of the heart before and after administration of the drug showed no significant changes.

SYMPTOMS DURING TREATMENT

There were no marked symptoms that could be ascribed to the local effects of phenylhydrazine hydrochloride. Gastric symptoms were not observed during the first three or four days of treatment. The various symptoms observed later were associated with jaundice and the rapid destruction of blood, and presented clinical features that would be expected during a hemolytic crisis, varying from very mild to very severe reactions. The symptoms associated with jaundice were mild. Definite pruritis was not present, although a little itching occurred in two cases. In one case there was a slight irritation of the bladder. In three cases there were gastric disturbances, nausea and vomiting; these were the cases in which there was marked destruction of blood. Anorexia was constant. Weakness, insufficient to prevent patients from being up and about, was invariably noted during the period of rapid destruction of blood.

One patient (case 4) developed jaundice, slight enlargement of the spleen and liver, abdominal distress and nausea. Then, rather suddenly, all these symptoms became very much worse and were associated with pain in the region of the spleen. Hematuria and slight hematemesis occurred. Undoubtedly a severe type of hemolytic crisis was present in this case, and in addition to this there may have occurred an infarction of the spleen and, possibly, also of the kidney. All these symptoms cleared up within a few days. In another case thrombosis of the basilic vein of the arm developed the day after treatment had been discontinued, following an intravenous injection to estimate hepatic function. In a third case a similar condition developed in a superficial vein of the left leg independent of any sort of injection or treatment (case 7). This thrombotic vein was resected and a microscopic examination showed a subacute thrombosis with erythrocytes, fibrin and a few fibroblasts. A month later the vein was palpable as a firm, hard cord. It is impossible to be certain that these instances of thrombosis are directly related to the phenylhydrazine treatment, as thrombosis is common in cases of untreated polycythemia vera, even when the blood volume is not extremely high. On the other hand, it is possible that thrombosis may have a direct relation to the rapid destruction of blood and the liberation of thromboplastic material during treatment.

14. Huffman, L. D.: Personal communication to the authors.

LATE EFFECTS OF TREATMENT

Patients have been traced after their dismissal from the clinic. The results have been satisfactory in all but one patient (case 2), who had marked hypertension. This did not decrease appreciably during treatment, and suboccipital headaches, mental irritability and weakness persisted. There was no evidence of deleterious effects from the use of phenylhydrazine in any of the cases. The maximal beneficial effects of treatment were evident in from three to six weeks after destruction of blood had ceased. Vertigo, fulness in the head, neuralgia, weakness and mental irritability disappeared in all but the one case noted. There were no significant changes in body weight. Intolerance to heat disappeared. The most striking improvement was the relief from pain. Two patients (cases 5 and 7) had had pain in the legs during exercise and clinical evidence of partial vascular obstruction (endarteritis obliterans). Complete relief was obtained while they were under observation, one month and one year, respectively. In case 6 there was lumbago of long standing with arthritic pains in the knees; the roentgen-ray examination showed a mild hypertrophic arthritis. Marked relief from pain followed the use of phenylhydrazine, but there was a gradual return of symptoms when the erythrocytes increased to approximately 6,000,000, with a return of the erythrosis and especially fulness of the head and vertigo. The length of time before the reappearance of symptoms has varied from three to six months. We have advised our patients to desist from further treatment until the symptoms became sufficiently troublesome to warrant it. The symptoms seem to be more important than the blood count in determining when further treatment is necessary.

DOSE OF THE DRUG

There is a considerable difference in patients with respect to their reaction to phenylhydrazine hydrochloride. The total amount of the drug given in order to obtain approximately the same effect in different patients varied from 3.4 to 7.6 Gm. Even when the dose is calculated on the basis of body weight and the amount of circulating hemoglobin destroyed, there is a marked difference in the amount of drug necessary. The average amount of hemoglobin destroyed by each gram of phenylhydrazine hydrochloride for each kilogram of body weight was 6 Gm. (table 15).

Examinations of the blood have not been made often enough, nor over long enough periods to draw positive conclusions concerning tolerance to the drug and the effect of repeated treatment with the drug. The original or initial dose has been repeated in each case. In case 1 a second course of the drug, totaling 9 Gm., was taken four months after the first course, without any noticeable result; the preparation was

probably inert. Two grams of a different brand of the drug gave symptomatic relief. Seven months later the erythrocytes numbered 6,000,000. In case 7 the initial total dose was repeated six months later, with complete relief from symptoms, but the patient did not become noticeably pale as he had after his first treatment. This man returned again a year after his first treatment and the original dose of 4.5 Gm. was as effective as formerly.

REPORT OF CASES

CASE 1.—*History.*—A man, aged 62, came to the clinic complaining chiefly of attacks of vertigo, which appeared suddenly and lasted a few seconds. They had persisted for two and one-half years, and had become increasingly frequent during the last year. He had also complained of numbness in the arms and shoulders, aching in various parts of the body, and general weakness. His appetite had become excessive and he suffered from constipation. Polyuria had been present for four years. He said that one maternal uncle had had a very red complexion.

Examination.—The patient was thin, weighing 132 pounds (59.9 Kg.). He was restless, consequently making purposeless motions, mentally irritable and somewhat melancholic. The mucous membranes were cyanotic and the skin of the face, hands and feet was reddish blue. Cold produced marked cyanosis, and the skin was dry and scaly. Cardiac dulness measured 10 cm. to the left, and the heart sounds were somewhat indistinct; an occasional extrasystole was present. The edges of the spleen and liver were both palpable. The peripheral blood vessels were not definitely sclerotic and the arteries of the feet seemed to be open. The retinal veins were markedly distended. The systolic blood pressure was 130, and the diastolic 85. The urine contained a trace of albumin and a few hyaline casts. The hemoglobin was 148 per cent by the acid hematin method (22.5 Gm. for each 100 cc.); the erythrocytes numbered 7,850,000, and the leukocytes 6,200. The relative viscosity of the blood was 13.2. The blood urea was 16 mg., creatinine 1.6 mg., and uric acid 2.9 mg. for each 100 cc. The total blood volume was 11,000 cc., or 180 cc. for each kilogram of body weight, whereas the cell volume by hematocrit was 67 per cent. The basal metabolic rate was + 37. A test of hepatic function by the dye method showed no retention, and the serum bilirubin was 0.7. The duodenal contents showed 1,000 units of urobilin and no urobilinogen. A fragility test of the red cells was normal. The clinical diagnosis was polycythemia vera.

Treatment.—The patient was given a total dose of 7.7 Gm. of phenylhydrazine hydrochloride over a period of thirty-five days. The total blood volume became reduced from 11,000 to 5,800 cc. (103 cc. for each kilogram of body weight), the hemoglobin from 22.5 to 11.5 Gm. for each 100 cc., and the erythrocytes from 7,850,000 to 2,640,000. Four grams of the drug was given first with only very slight effect. An additional 3.7 Gm. was administered, during which time the destruction of blood became marked. Repeated tests of hepatic function by the dye method showed no retention following treatment, while the phenolsulphonphthalein estimation at the termination of treatment was 55 per cent. The basal metabolic rate had fallen from + 37 to — 4. Symptomatically the improvement was striking: the patient was quite free from his former symptoms, vertigo, mental irritability and restlessness having entirely disappeared. He was definitely pale with a trace of icterus.

This was the first case under our observation treated by phenylhydrazine. The result was very satisfactory despite the development of rather marked anemia. We were unable to demonstrate any effect on the function either of the liver or the kidney. The patient's symptoms recurred in six months and a similar course of treatment was given

TABLE 1.—*The Blood (Case 1)*

Date, 1924	Hemoglobin: Grams, per Cent	Hemoglobin: Per Cent	Erythrocytes, Millions	Leukocytes	Relative Viscosity (Hess)	Cells by Hematocrit, per Cent	Blood: Volume, Cc.	Blood: Cc. for Each Kg. of Body Weight	Plasma: Volume, Cc.	Plasma: Cc. for Each Kg. of Body Weight	Total Circulating Volume of Hemoglobin, Gm.	Serum Bilirubin, Mg.	Total Dose of Drug, Gm.	Clinical Notes
12/15	22.5	148	7.85	6,200	13	67	11,000	183	3,640	60	2,470	1.7	...	Body weight, 60 Kg.
12/28	21.4	140	7.20	20,600	..	63	7,970	142	2,950	52	1,700	...	1.9	
1925														
1/14	19.9	130	5.70	1,700	..	65	9,900	173	3,460	60	1,970	...	3.4	
2/ 4	16.0	105	5.27	16,000	8	56	8,520	157	3,750	69	1,360	2.45	4.4	Pallor 1
2/11	12.4	81	4.62	.....	..	40	6,500	116	3,900	70	800	...	7.6	Slight jaundice
2/16	11.5	75	2.64	.....	..	39	5,800	103	3,530	63	660	1.26	...	Patient dismissed; symptomatically much improved
4/ 4	18.0	118	3.32	17,400	..	..	.....	...	.....	..	.....	...	...	Second course of drug (9 Gm.) with very little effect; inferior drug used
11/14	18.2	119	6.53	11,700	..	..	.....	...	.....	..	.....	...	2.0*	Patient well; no recurrence of symptoms

* Taken during July.

at home with satisfactory result. Ten months after the first period of treatment another course was given; however, no increase in the dosage was necessary in the subsequent treatments to produce a satisfactory relief from symptoms (tables 1 and 2). The patient stated in a recent letter that 0.3 Gm. a week would keep him symptomless.

CASE 2.—*History.*—A man, aged 56, came to the clinic because he had had headaches and stomach trouble for the last two years. Pains in the right shoulder and arm had been diagnosed neuritis. He was also told that he had high blood pressure. Later severe attacks of pain accompanied by nausea and vomiting had occurred in the occiput every three or four days; these persisted up to the time of examination. He had complained of ringing in the ears, severe vertigo, blurring of vision, and dyspnea on moderate exercise. Constipation and slight loss of appetite had been constant during the last year. There was no definite family history of polycythemia.

Examination.—The patient was well nourished, weighing 150 pounds (68 Kg.). The systolic blood pressure was 192, and the diastolic 140. The face, hands and feet were reddish purple and cold, but arterial pulsation was normal. The mucous membranes of the mouth and tongue were markedly cyanotic. The spleen was

TABLE 2.—*Renal and Hepatic Function (Case 1)*

	Renal Function			Hepatic Function		Urine							
								Grade 0 to 4					
Date, 1924	Phenolsulphonphthalein, per Cent	Blood Urea, Mg.	Blood Creatinine, Mg.	Dye Retention, Grade 0 to 4	Serum Bilirubin, Mg.	Color	Bile	Albumin	Casts	Erythrocytes	Leukocytes	Urobilin	Total Dose of Drug, Gm.
12/18	40	16	1.6	0	0.7	....	..	1	1	0	1	0	...
1925													
2/ 4	55	45	1.8	0	2.45	Black	+	1	0	1	1	0	4.4
2/12	..	48	2.2	...	1.26	Dark brown	+	1	0	0	1	0	7.7

just palpable; the liver was not felt. The peripheral vessels were markedly tortuous and somewhat thickened. The retinal arteries were constricted and the veins enlarged. There were edema of the disks and small retinal hemorrhages and exudates. The urine contained a moderate trace of albumin and a few erythrocytes. The specific gravity varied from 1.010 to 1.026. The phenolsulphonphthalein secretion was 55 per cent in two hours. The hemoglobin was 29.4 Gm. for each 100 cc. of blood; the erythrocytes numbered 8,530,000, and the leukocytes 6,400. The fragility of the erythrocytes was normal. The platelets were diminished in number; the coagulation time by the Boggs method was three minutes, the bleeding time one minute, and the relative viscosity 12. A study of the chemistry of the blood showed 45 mg. of urea, 1.8 mg. of creatinine, and 2.9 mg. of uric acid for each 100 cc. of blood. The blood sugar was 0.089 mg. for each 100 cc. of blood. Tests of hepatic function showed no retention by the dye method; the serum bilirubin was 0.9, and the fructose tolerance test was normal. The total blood volume was 12,400 cc. (190 cc. for each kilogram of body weight). By hematocrit there was 72 per cent erythrocytes. The vessels of the leg were normal from roentgenologic examination. A diagnosis was made of polycythemia vera, severe essential hypertension with arteriosclerosis, and cardiac hypertrophy with slight insufficiency.

Treatment.—The patient was given a total dose of 6.4 Gm. of phenylhydrazine over a period of sixteen days. During the treatment, destruction of blood was marked, the total volume being reduced to 5,050 cc. (81 cc. for each kilogram of

TABLE 3.—*The Blood (Case 2)*

Date, 1925	Hemoglobin: Grams, per Cent	Hemoglobin: Per Cent	Erythrocytes, Millions	Leukocytes	Relative Viscosity (Hess)	Cells by Hematocrit, per Cent	Blood: Volume, Cc.	Blood: Cc. for Each Kg. of Body Weight	Plasma: Volume, Cc.	Plasma: Cc. for Each Kg. of Body Weight	Total Circulating Volume of Hemoglobin, Gm.	Serum Bilirubin, Mg.	Total Dose of Drug, Gm.	Clinical Notes
4/12	29.4	193	8.53	6,700	15	72	12,400	190	3,460	51	3,640	0.9	...	Body weight, 68 Kg.; blood pressure, 190/140
4/28	23.4	153	6.12	14,900	12	70	11,100	173	3,300	52	2,590	2.4	2.6	
5/ 6	20.8	136	4.97	.....	9.6	60	8,750	136	3,500	55	1,820	...	5.3	May 2, headaches disappeared; May 10, sclera, jaundice 1
5/15	12.5	82	3.31	16,100	4	37	5,050	81	3,180	51	630	4.3	6.4	
5/19	9.5	62	2.20	14,700	..	..	.....	...	.....	..	.....	...	...	Phlebitis of left basilic vein; blood pressure, 196/120; weight, 69 Kg.
5/26	....	...	....	.....	..	..	.....	...	.....	..	.....	...	...	Patient dismissed
6/17*	....	75	3.40	8,000	..	..	.....	...	.....	..	.....	...	...	Color normal; occasional mild vertigo

* Following dismissal tests of the blood were carried out by Dr. Thor Jager, Wichita, Kan.

body weight), and the cell volume was 37 per cent by hematocrit. The erythrocytes numbered 4,520,000 when the drug was stopped. However, the number of erythrocytes became further reduced to 2,180,000, and the hemoglobin to 9.5 Gm. within a period of ten days after treatment was discontinued. Then evidence of destruction of blood ceased; during this period the blood urea increased to 72 mg. for each 100 cc. of blood, the creatinine to 3.8 mg., and the serum bilirubin to 4.3 mg. At this time the patient was definitely jaundiced and had bile in the urine. The phenolsulphonphthalein secretion at the time of the patient's dismissal was 35 per cent in two hours, and the test of hepatic function by the dye method showed no retention. The fructose tolerance test was unchanged. Thrombosis of the left basilic vein developed on the tenth day of treatment, following the injection of bromsulphalein, but subsided in three weeks. The systolic blood pressure following the initial period of rest was reduced to 180, and the diastolic to 120. After completion of treatment the systolic blood pressure was 196 and the diastolic 120; this level was maintained during the subsequent period of observation. Clinical and symptomatic improvement was very definite following treatment. The severe headaches and dizziness disappeared. The patient was allowed to return home and subsequent reports were kindly furnished by his physician. One month after his dismissal the erythrocytes numbered 2,800,000, and the leukocytes 12,000; hemoglobin by the Sahli method was 65 per cent. The phenolsul-

TABLE 4.—*Renal and Hepatic Function (Case 2)*

	Renal Function			Hepatic Function		Urine						
								Grade 0 to 4				
Date, 1925	Phenol-sulphon-phthalein, per Cent	Blood Urea, Mg.	Blood Creat-inine, Mg.	Dye Re-tention Grade 0 to 4	Serum Bili-rubin, Mg.	Color	Bile	Uro-bilin	Albu-min	Casts	Eryth-ro-cytes	Leuko-cytes
4/18	55	45	1.9	0	0.9	.....	0	0	1	0	0	1
4/28	60	38	1.6	...	....	.....	0	...	1	Granu-lar 1	1	1
5/ 1	..	..	...	0	2.4	Dark brown	...	...	...	...	...	...
5/ 6	35	52	2.2	...	....	Black	+	...	1	0	0	1
5/15	..	72	3.8	...	4.3	Less dark	+	...	1	0	1	1

phonphthalein excretion was 60 per cent for two hours, and the blood urea was 35 mg. for each 100 cc. of blood. Two weeks later the erythrocytes had increased to 3,400,000 and the leukocytes numbered 8,000; the hemoglobin was 75 per cent. Two months later the patient wrote that he felt his symptoms recurring, and he was advised to repeat the treatment. Symptoms recurred again six months after the second treatment.

The interesting points in the review of this case are: (1) the lack of response of the blood pressure to a marked reduction in the circulating volume and viscosity of the blood; (2) relief for six months from symptoms that would ordinarily be ascribed to the hypertension, and (3) the absence of any demonstrable renal injury following treatment by phenylhydrazine when the presence of definite arteriosclerosis with probable pathologic changes in the kidneys would permit of marked susceptibility of this organ to toxic agents. There was no demonstrable hepatic damage, according to the tests of hepatic function. The development of marked anemia following the discontinuance of phenylhydrazine is also to be noted (tables 3 and 4).

CASE 3.—*History.*—A man, aged 43, came to the clinic because of vomiting, general weakness, fatigue, lumbago and occasional headaches, symptoms that began three years before, following dengue fever. He had been intolerant to heat and had become very nervous and excitable. During the preceding year he had vomited every morning. Eighteen months previously the extraction of teeth had been followed by a brisk hemorrhage which left him weak but symptomatically much improved. He had lost 20 pounds (9 Kg.). For six months his symptoms had been getting worse until at the time of admission he could walk but short distances. His wife had noticed an increasing purplish color of the skin. There was no record in the family history of a similar condition.

Examination.—The patient was well developed and weighed 147 pounds (66.7 Kg.). The face and hands were very red and the conjunctiva injected. The mucous membranes of the mouth were reddish blue. The heart measured 11 cm. to the left. The systolic blood pressure was 160, and the diastolic 120. The spleen was enlarged to the navel, 13 cm. below the costal margin, and was not tender. The liver was not palpable. There were external hemorrhoids. The urine was normal. The acid hematin hemoglobin was 180 per cent; the erythrocytes numbered 7,480,000, and the leukocytes 6,700. The whole blood volume was 13,530 cc. (202 cc. for each kilogram of body weight), and the erythrocytes by hematocrit were 69 per cent. The number of platelets was normal. The coagulation time was six minutes by the Boggs method, the bleeding time one and one-half minutes, and the relative viscosity of the blood much increased, 11.8. The phenolsulphonphthalein excretion was 65 per cent in two hours. The fragility of the erythrocytes was normal. The retinal veins were markedly engorged and cyanotic, and the retinal arteries mildly sclerotic. The diagnosis was polycythemia vera.

Treatment.—The patient received a total dosage of 6.1 Gm. of phenylhydrazine hydrochloride during a period of sixteen days. There was a sharp decrease in the circulating blood volume and at the end of treatment very definite anemia. The platelet count throughout the entire period of observation was normal or slightly below normal, and marked leukocytosis developed. There was a decrease in the circulating blood volume of 5,000 cc., or approximately 50 per cent. An extreme reduction in hemoglobin and red cells occurred. Marked jaundice developed. The spleen increased in size during the height of destruction of blood, and the liver became palpable. During the peak of destruction the patient complained of pain in the epigastrium, extreme weakness and slight nausea. The urine became dark red, but no erythrocytes were found on microscopic examination. The blood urea increased and the phenolsulphonphthalein excretion decreased to 25 per cent. After the drug had been discontinued, destruction of blood continued for six days, but the patient's general condition rapidly improved and he felt quite normal, except for moderate weakness at the time of dismissal. The spleen had become reduced to one-half its former size. The liver was 5 cm. below the costal margin. Subsequent blood counts were obtained through the courtesy of his home physician. A recurrence of symptoms took place three months after his dismissal, at which time erythrocytes numbered 8,000,000 for each cubic millimeter. A course of phenylhydrazine of the same dosage as the initial treatment gave complete relief from symptoms (tables 5 and 6).

The patient at the time of admission showed marked nervous irritability, restlessness and extreme weakness. The spleen was unusually large, extending to the navel. In spite of the extreme manifestations of the disease a prompt reduction in the blood volume and amelioration of the symptoms occurred. A severe anemia developed, without, however, symptoms that would ordinarily be associated with anemia, and from which the patient rapidly recovered. The renal function, according to the dye test, decreased from 65 to 25 per cent. The spleen

TABLE 5.—*The Blood (Case 3)*

Date, 1925	Hemoglobin: Grams, per Cent	Hemoglobin: Per Cent	Erythrocytes, Millions	Leukocytes	Relative Viscosity (Hess)	Cells by Hematocrit, per Cent	Blood: Volume, Cc.	Blood: Cc. for Each Kg. of Body Weight	Plasma: Volume, Cc.	Plasma: Cc. for Each Kg. of Body Weight	Total Circulating Volume of Hemoglobin, Gm.	Serum Bilirubin, Mg.	Total Dose of Drug, Gm.	Clinical Notes
7/24	27.4	180	7.4	6,700	16	69	13,530	202	41,000	62	3,700	1.7	...	Fructose tolerance test negative; body weight, 67 Kg.
8/ 5	24.4	160	7.4	23,600	11.8	68	10,600	160	34,000	51	2,580	....	1.6	Jaundice 1; red fading
8/ 7	.....	...	6.22	19,300	..	..	.....	...	.....	..	.....	6.9	...	
8/10	24.0	157	6.28	.....	9.2	54	8,600	138	35,000	55	2,060	3.5	3.2	
8/17	14.0	92	4.25	50,300	5.6	37	5,950	93	3,700	58	830	5.3	...	Pain in epigastrium; weakness; insomnia
8/21	8.6	56	2.65	41,700	..	..	.....	...	.....	..	.....	3.67	...	Spleen larger, not tender; jaundice 2
8/26	6.6	43	2.03	40,800	2.4	15	5,500	87	4,670	72	360	1.87	6.0	Feeling much better except for some weakness
8/31	4.5	29	2.0	31,000	3.3	..	.....	...	.....	..	.....	...	...	Spleen reduced; red color returning; weakness; weight, 67 Kg.
11/ 5*	...	115	8.8	19,500	..	..	.....	...	.....	..	.....	...	...	

* Blood count made by Dr. Robert Harris of Miami, Fla.

became reduced to half its former size. A second course of treatment with the same dosage became necessary three months later, and was followed by satisfactory results.

CASE 4.—*History.*—A woman, aged 31, came to the clinic complaining of indigestion and recurring attacks of migraine, consisting of severe frontal headaches, vertigo, and specks of fire before the eyes, which were relieved by vomiting but had continued for the last six years. She slept poorly; was easily fatigued, and was constipated. An abdominal exploration and cholecystectomy had been performed two years previously elsewhere. A tumor was then noted in the left upper quadrant. The family history contained nothing of significance.

Examination.—The patient was thin and asthenic with skin moderately pigmented and dusky, reddish blue, especially on the face, neck, hands and arms. The finger nails were cyanotic and the pharynx and mucous membranes of the mouth were a deep reddish blue. The size of the heart and the heart sounds were normal. The systolic blood pressure was 120, and the diastolic 90. The spleen extended 4 cm. below the costal margin. The liver was not palpable. The peripheral arteries were soft and the veins distended. The nail capillaries were distended and the number of open capillaries for each square millimeter of skin on the back of the hands was about double the normal number. The fundi were essentially normal except that the retinal veins were a little darker and fuller

TABLE 6.—*Renal and Hepatic Function (Case 3)*

	Renal Function			Hepatic Function		Urine				
							Grade 0 to 4			
Date, 1925	Phenolsulphonphthalein, per Cent	Blood Urea, Mg.	Blood Creatinine, Mg.	Dye Retention, Grade 0 to 4	Serum Bilirubin, Mg.	Color	Albumin	Casts	Erythrocytes	Leukocytes
7/24	65	27	1.5	0	1.7	.....	1	Hyalin, 1	0	1
8/ 7	..	39	...	0	6.8	.....	1	...	...	1
8/13	25	42	...	0	4.9	Dark brown	1	...	1	1
8/17	25	174	3.4	...	5.3	Dark brown	1	...	1	1
8/19	..	203	3.2	...	...	Dark brown	Trace	...	...	1
8/22	25	52	...	0	3.6	Dark brown	2	...	...	1
8/26	..	52	1.5	0	1.87	Clear ring	...	...	...	...
8/28	..	36	...	...	...	.....	...	...	...	...
8/31	..	25	...	...	...	.....	...	...	...	...

than usual. The range of the specific gravity of the urine was normal. The sediment contained a few erythrocytes and 50 leukocytes to the low power field. The phenolsulphonphthalein excretion was 50 per cent in two hours. The erythrocytes numbered 6,890,000, and the leukocytes 9,500; the hemoglobin was 19.4 Gm. for each 100 cc. of blood, and 127 per cent by the acid hematin method. The whole blood volume was 7,700 cc. (167 cc. for each kilogram of body weight), and the erythrocytes by hematocrit were 71 per cent. The platelet count was normal. The coagulation time by the Boggs method was eight minutes, and the bleeding time one minute (table 7). The diagnosis was polycythemia vera and migraine.

Treatment.—During the height of destruction of blood the patient became weak, vomited blood-streaked material, and complained of severe soreness in the left upper quadrant. The urine contained macroscopic blood; the spleen was markedly tender, and jaundice developed. Within five days after treatment was stopped, practically all symptoms had subsided and splenic tenderness had disappeared. The basal metabolic rate which was + 19 at the beginning of treatment later was + 37 and + 27, and finally + 15 at the time the patient was dismissed.

TABLE 7.—*The Blood (Case 4)*

Date, 1925	Hemoglobin		Erythrocytes, Millions	Leukocytes	Cells by Hematocrit, per Cent	Blood		Plasma		Total Circulating Volume of Hemoglobin, Gm.	Serum Bilirubin, Mg.	Total Dose of Drug, Gm.	Clinical Notes
	Grams, per Cent	Per Cent				Volume, Cc.	Cc. for Each Kg. of Body Weight	Volume, Cc.	Cc. for Each Kg. of Body Weight				
6/20	19.4	127	6.89	9,500	71	7,700	167	2,250	48	1,490	1.5	...	Weight, 46 Kg.
6/29	19.0	125	6.90	9,600	..	7,800	160	2,970	63	1,480	5.3	2.0	Jaundice 1
7/ 6	12.2	80	5.60	12,000	37	4,800	104	3,020	65	580	5.7	3.4	Blood vomited; marked soreness over spleen; infarct (?)
7/ 8	....	...	4.76	15,600	..	.....	...	.....	..	.....	...	...	Jaundice 2; pallor; weakness, headache, vomiting, nausea
7/10	....	...	4.20	16,900	..	.....	...	.....	..	.....	...	...	Recurrence of migraine attacks
7/11	8.7	57	4.20	16,900	23	4,380	102	3,397	79	380	3.9	...	
7/15	7.0	46	2.50	17,500	..	.....	...	.....	..	.....	...	...	Spleen smaller; tender 1, 2 cm. below costal margin
7/20	8.4	55	2.04	9,000	23	4,020	80	3,100	69	330	...	...	Feeling well
10/ 3*	....	130	6.60	.....	..	.....	...	.....	..	.....	..	...	No definite symptoms; feeling well; weight, 56 Kg.

* Courtesy of Dr. John Valens, Saskatoon, Saskatchewan.

At dismissal the patient felt fairly strong in spite of her anemia; the symptoms had entirely disappeared. A total dose of 3.5 Gm. of phenylhydrazine was given during a period of fourteen days. Four months later she wrote that she was feeling well, but had had several attacks of migraine (tables 7 and 8).

The chief complaint in this instance was of an aggravation of preexisting migraine. The number of open capillaries for each square millimeter of skin on the back of the hand was about double the normal number. A severe hemolytic crisis occurred during treatment. Later the more constant symptoms disappeared but the attacks of migraine recurred.

CASE 5.—*History.*—A man, aged 64, entered the clinic Nov. 10, 1925, complaining of pain in the right leg. Two years previously, pain, which was related to exercise, began in the muscles of the left leg, especially in the left foot and calf. Eighteen months later the left lower leg was amputated, elsewhere, on account of pain and impending gangrene. Since that time he had had severe pain in the stump, although not severe enough to prevent sleep. Similar, less severe symptoms had developed in the right leg and foot during the last year. His leg fatigued easily, and when he walked an ache developed in the ball of the foot. The foot was extremely cold for several days at a time. Bluish spots appeared on the skin. He

TABLE 8.—*Renal and Hepatic Function (Case 4)*

	Renal Function			Hepatic Function		Urine						
									Grade 0 to 4			
Date, 1925	Phenolsulphonphthalein, per Cent	Blood Urea, Mg.	Blood Creatinine, Mg.	Dye Retention Grade 0 to 4	Serum Bilirubin, Mg.	Color	Bile	Urobilin	Albumin	Casts	Erythrocytes	Leukocytes
6/17	50	11	1.1	0	1.5	.....	...	...	...	0	1	0
6/23	50	..	...	...	....	Dark	Trace	...	1	0	1	2
6/27	..	..	...	...	5.3	Dark	Trace	...	1	0	1	2
7/ 7	65	69	1.5	0	5.7	Dark	Trace	+	2	0	2	1
7/11	..	36	1.3	...	3.9	Dark	.....	...	1	0	1	2
7/20	50	..	...	...	....	.....	0	0	1	0	0	2

had been worried about his condition, fearing loss of his right foot. His father had died of a stroke at the age of 74.

Examination.—The patient was fairly well preserved, and weighed 140 pounds (63.5 Kg.). His face and hands were definitely red and his nose cyanotic. The mucous membranes were cyanotic and the sclerotics were injected. The heart measured 10 cm. to the left; the sounds were of a good quality with a marked accentuation of the aortic second sound. The aorta was palpable in the episternal notch, and there was bilateral pulsation of the carotids. The systolic blood pressure was 204, and the diastolic 120. The spleen measured 5 cm. and the liver 6 cm. below the costal margin in the nipple line on full inspiration. They were firm to touch, but not tender. Pulsations were constant in the right femoral and popliteal muscles, and intermittent in the dorsalis pedis and posterior tibial muscles. The right foot was reddish blue and cold, with a sharp demarcation of the temperature line at the ankle. The circulatory efficiency tests of the right leg showed a marked bluish pallor at 180 degrees, whereas at 0 there was mild reactionary rubor. The retinal veins were moderately engorged and the arteries small and contracted. The nail-fold capillaries were long, narrow and arteriosclerotic in type, with slight engorgement of the venous limb. Roentgenologic examination of the right leg showed definite calcification of the vessels. An electrocardiogram showed no significant changes. The maximal specific gravity of the urine was 1.022. The phenolsulphonphthalein excretion was 40 per cent in two hours. There were 24.5 Gm. of hemoglobin for each 100 cc. of blood; the erythrocytes numbered 5,020,000,

TABLE 9.—*The Blood (Case 5)*

Date, 1925	Hemoglobin: Grams, per Cent	Hemoglobin: Per Cent	Erythrocytes, Millions	Leukocytes	Cells by Hematocrit, per Cent	Blood: Volume, Cc.	Blood: Cc. for Each Kg. of Body Weight	Plasma: Volume, Cc.	Plasma: Cc. for Each Kg. of Body Weight	Total Circulating Volume of Hemoglobin, Gm.	Serum Bilirubin, Mg.	Total Dose of Drug, Gm.	Clinical Notes
11/11	24.5	161	5.02	13,000	60	8,500	136	3,430	54	2,100	...	...	Weight, 63 Kg.; face, red 2
11/16	....	...	....	.....	..	.....	...	.....	..	.....	0.7	...	
11/27	....	...	4.99	.....	..	.....	...	.....	..	.....	...	2.8	Urine, dark brown
11/30	....	...	4.97	18,000	..	.....	...	.....	..	.....	...	...	
12/ 7	....	...	....	.....	32	4,550	75	3,070	51	400	6.0	4.2	Jaundice (?); skin itching; spleen larger (?)
12/10	8.8	57	2.99	27,500	..	.....	...	.....	..	.....	...	...	Pallor 2; absolute relief from pain in legs
12/14	....	...	3.10	23,500	..	.....	...	.....	..	.....	...	..	Weakness; weight, 62 Kg.

and the leukocytes 13,000. The volume of the whole blood was 8,580 cc. (136 cc. for each kilogram of body weight), and the erythrocytes by hematocrit were 60 per cent. The diagnosis was polycythemia vera, essential hypertension, generalized arteriosclerosis, and endarteritis obliterans of the arteries of the leg.

Treatment.—A total dose of 4.3 Gm. of phenylhydrazine hydrochloride was given during a period of fifteen days. The effect was definite. The usual leukocytosis appeared soon after starting the drug. There was a gradual reduction in blood volume of approximately 50 per cent, from 8,580 to 4,550 cc. The urine became dark brown five days after the administration of the drug. As the volume of blood decreased, the pain in the legs diminished. Jaundice and an increase in the serum bilirubin developed. No change in the size of the liver or spleen was noted during treatment. The phenolsulphonphthalein output decreased to 15 per cent. There was no increase in the blood urea. At the time the patient was dismissed he was completely relieved from pain in the right foot and left stump. He felt somewhat weak, but said he had not felt better for years. The systolic blood pressure dropped to 160, and the diastolic to 90, as a result of his initial rest in bed; a further reduction occurred during treatment (systolic 130, and diastolic 70).

The points of interest in this case are: (1) the evidence of endarteritis obliterans with pain out of proportion to the demonstrable vascular occlusion; (2) the hypertension of the essential type with considerable arteriosclerosis, and (3) complete relief of pain in the legs and a reduction in the hypertension with treatment by phenylhydrazine (tables 9 and 10).

TABLE 10.—*Renal and Hepatic Function (Case 5)*

	Renal Function			Hepatic Function		Urine					
									Grade 0 to 4		
Date, 1925	Phenol-sulphon-phthalein, per Cent	Blood Urea, Mg.	Blood Creatinine, Mg.	Dye Retention Grade 0 to 4	Serum Bilirubin, Mg.	Color	Bile	Urobilin	Albumin	Casts	Erythrocytes	Leukocytes
11/11	40	43	1.7	1	0.7	.....	...	...	1	...	...	1
11/24	..	..	...	...	....	.....	...	0	0	0	0	0
11/26	..	..	...	...	....	Dark brown	...	+	...	...	...	...
12/ 1	..	..	...	...	....	Dark brown	...	+	0	1	...	...
12/ 6	15	..	...	...	6.0	.....	...	+	1	0	1	1
12/11	..	42	...	...	....	.....	Trace	+	1	1	...	...
12/15	15	33	...	...	....	Light brown	...	...	...	...	...	...

CASE 6.—*History.*—A man, aged 55, entered the clinic Dec. 1, 1925, with a complaint of weakness, pain and aching in the arms, shoulders, knees and lower lumbar regions, and mild nocturia and dysuria, of six or seven years' duration. Tonsillectomy three years previously had afforded some relief. His eyes had been somewhat bloodshot for the last three years, and his wife had noticed increasing redness of his face, especially for six or seven months. Sweating was excessive in the warm weather, and the previous summer he had not been able to work because of increasing fatigue and weakness. He became cold easily and warmed up with difficulty, but felt suffocated in a warm room. His appetite had been excessive for several years.

Examination.—The patient was well nourished and robust, weighing 185 pounds (83.9 Kg.). His appearance was very striking. The face, neck, hands and feet were markedly cyanotic. The mucous membranes were markedly reddish blue and the conjunctiva of the sclerotics was fiery red. The skin over the entire body was moist and soft. The heart measured 9.5 cm. to the left, the arch 6 cm.; the

TABLE 11.—*The Blood (Case 6)*

Date, 1925	Hemoglobin		Erythrocytes, Millions	Leukocytes	Relative Viscosity (Hess)	Cells by Hematocrit, per Cent	Blood		Plasma		Total Circulating Volume of Hemoglobin, Gm.	Serum Bilirubin, Mg.	Total Dose of Drug, Gm.	Clinical Notes
	Grams, per Cent	Per Cent					Volume, Cc.	Cc. for Each Kg. of Body Weight	Volume, Cc.	Cc. for Each Kg. of Body Weight				
12/ 2	25.2	166	6.04	9,900	14.4	..	14,700	180	3,670	46	3,700	...	...	Weight, 84 Kg.; cyanosis 3 of face and hands
12/ 8	26.0	171	7.00	10,200	..	75	.....	...	.....	..	.....	...	...	
12/18	21.0	138	5.18	12,100	..	..	.....	...	.....	..	.....	7.6	4.2	Jaundice 2
12/22	14.0	92	5.00	16,500	6.0	43	6,940	90	3,950	52	970	7.3	5.3	Jaundice 2; pallor 2
12/24	12.5	82	4.96	2,100	..	..	.....	...	.....	..	.....	...	...	Superficial phlebitis of both legs
12/28	11.0	72	....	.....	..	..	.....	...	.....	..	.....	...	...	Jaundice 1; weakness; skin itchy
1926 1/ 4	8.0	52	....	.....	3.1	24	5,650	75	4,200	57	450	1.8	...	Spleen much reduced in size; pallor 2

sounds were normal. The systolic blood pressure was 140, and the diastolic 100. The lower lumbar spine showed a fixation of about 80 per cent, with some localized tenderness. The spleen measured 4 cm. below the costal margin in the anterior axillary line. The liver measured 4.5 cm. below the costal margin in the nipple line. The specific gravity of the urine was normal, but there was a moderate amount of albumin and occasional erythrocytes in the urine; the phenolsulphonphthalein excretion was 40 per cent in two hours. The blood urea was 18 mg. for each 100 cc. The Wassermann reaction was negative. The hemoglobin was 166 per cent by the acid hematin method; the erythrocytes numbered 6,040,000, and the leukocytes 9,900. The volume of the whole blood was 14,700 cc. (180 cc. for each kilogram of body weight); the erythrocytes by hematocrit were 75 per cent. The relative viscosity of the whole blood was 14.4. The retinal veins were considerably distended. Roentgenograms did not show arteriosclerosis of the vessels of the leg; there was slight arthritis of the knee joints. The nail-fold capillaries were engorged, the flow was slow, and there were many open capillaries. The diagnosis was polycythemia vera and chronic infectious arthritis of the hypertrophic type (tables 11 and 12).

TABLE 12.—*Renal and Hepatic Function (Case 6)*

	Renal Function			Hepatic Function		Urine						
									Grade 0 to 4			
Date, 1925	Phenolsulphonphthalein, per Cent	Blood Urea, Mg.	Blood Creatinine, Mg.	Dye Retention Grade 0 to 4	Serum Bilirubin, Mg.	Color	Bile	Urobilin	Albumin	Casts	Erythrocytes	Leukocytes
12/ 3	40	18	...	0	....	.....	...	...	3	...	2	1
12/ 8	25	..	...	...	....	.....	...	...	...	...	...	...
12/11	..	..	...	...	....	.....	...	...	2	1	0	1
12/14	15	..	...	...	....	.....	...	...	...	...	...	...
12/16	..	..	...	...	....	Dark	++	+	2	...	0	1
12/17	..	45	1.4	...	7.6	.....	...	...	...	...	...	...
12/23	35	73	1.7	...	....	.....	...	...	...	...	...	...
12/28	..	73	...	0	....	Less dark	...	...	...	...	...	...

Treatment.—The patient received a total dose of 5.4 Gm. of phenylhydrazine hydrochloride during a period of eighteen days. During the height of destruction of blood he complained of dull continuous pain in both lower legs, which was due to superficial phlebitis. There was no rise in temperature. The redness and pain subsided after ten days, leaving the veins like hard fibrous cords. Pathologic examination of a resected segment of vein revealed a subacute venous thrombosis. Serum bilirubin was increased after four days of treatment, and definite clinical jaundice appeared after 4.2 Gm. of the drug had been given. Leukocytosis and a rapid decrease in the hemoglobin and erythrocytes followed the administration of 5.3 Gm. The hemoglobin decreased 30 per cent after the drug was stopped. There was an increase in the blood urea and slight diminution of the phenolsulphonphthalein excretion. The patient felt weak during the period of destruction of blood but there were no other untoward symptoms. The spleen showed no change in size or tenderness. The urine became dark on the fourth day of treatment, and was slightly dark at the time of the patient's dismissal. The pain in the joints disappeared under treatment.

This case is an example of extreme manifestations of the disease. The volume of the whole blood was very high, 14,700 cc. However, a total dosage of only 5.4 Gm. of phenylhydrazine hydrochloride was necessary to bring about a very marked reduction in the blood volume and improvement of the symptoms. Arthritis was present with pains in the joints; the pain disappeared during treatment.

TABLE 13.—*The Blood (Case 7)*

Date, 1925	Hemoglobin: Grams, per Cent	Hemoglobin: Per Cent	Erythrocytes, Millions	Leukocytes	Relative Viscosity (Hess)	Cells by Hematocrit, per Cent	Blood: Volume, Cc.	Blood: Cc. for Each Kg. of Body Weight	Plasma: Volume, Cc.	Plasma: Cc. for Each Kg. of Body Weight	Total Circulating Volume of Hemoglobin, Gm.	Serum Bilirubin, Mg.	Total Dose of Drug, Gm.	Clinical Notes
2/ 6	19.0	125	5.49	7,700	..	..	.....	...	.....	..	.....	...	...	Spleen enlarged 1; face red 1
2/ 9	19.0	125	....	.....	..	58	8,350	112	3,500	47	1,580	1.7	1.5	Weight, 73 Kg.; urine, dark brown
2/23	....	...	5.93	9,900	10.4	..	.....	...	.....	..	.....	...	2.7	
2/26	16.0	105	4.09	7,400	..	..	.....	...	.....	..	.....	3.6	3.6	Jaundice 1; skin itching
3/ 2	11.6	76	2.73	15,600	..	40	6,820	93	4,090	56	790	4.8	4.5	Pallor 2; jaundice 1; disappearance of pain in legs
3/10	6.5	42	2.02	13,300	3.5	23	6,150	84	4,740	65	400	1.44	...	
3/14	8.3	54	2.26	12,600	..	..	.....	...	.....	..	.....	...	...	Feeling well; appetite increasing; no symptoms
3/17	8.6	56	2.49	12,100	..	..	.....	...	.....	..	.....	0.13	...	
3/22	....	...	2.52	11,200	..	..	.....	...	.....	..	.....	...	...	
3/23	....	...	2.56	9,200	..	..	.....	...	.....	..	.....	..	...	Weight, 72 Kg.
1926 1/ 6*	21.4	140	5.52	9,600	10.6	64	9,330	129	3,360	46	1,996	0.8	...	

* Course of phenylhydrazine (total of 4.5 Gm.) during June, 1925.

CASE 7.—*History.*—A man, aged 58, came to the clinic complaining of weakness in the legs of seven or eight years' duration. The symptoms first began after standing five or ten minutes. Later, walking and cold aggravated the condition. He had had slight dyspnea on exertion and ringing in the left ear for two years. He had always had a high color, but this had been more noticeable in the last five years.

Examination.—The patient weighed 165 pounds (74.8 Kg.). His face, neck and hands were very red; his feet and scrotum less red. The mucous membranes were slightly cyanotic, and the tip of the nose markedly so. The spleen was just palpable. The retinal veins were full and the arteries showed fibrosis. Roentgenologic examination of both lower legs showed marked arteriosclerosis of the vessels. The urine was not abnormal and the phenolsulphonphthalein excretion was 50 per cent, while the blood urea was 26 mg. The systolic blood pressure was 172, and the diastolic 106. There were 19 Gm. of hemoglobin for each 100 cc. of blood; the erythrocytes numbered 5,490,000, and the leukocytes 7,700. The relative viscosity of the whole blood was 10.4. The total blood volume was 8,350 cc. (112 cc. for each kilogram of body weight). The red cell volume was 58 per cent by hematocrit. The diagnosis was polycythemia vera, mild essential hypertension with arteriosclerosis, and endarteritis obliterans incomplete of both feet.

TABLE 14.—*Renal and Hepatic Function (Case 7)*

	Renal Function			Hepatic Function		Urine					
									Grade 0 to 4		
Date, 1925	Phenol-sulphon-phthalein, per Cent	Blood Urea, Mg.	Blood Creat-inine, Mg.	Dye Re-tention Grade 0 to 4	Serum Bili-rubin, Mg.	Color	Bile	Uro-bilin	Albu-min	Casts	Eryth-ro-cytes	Leuko-cytes
2/ 6	50	26	...	...	....	.....	...	...	0	...	...	1
2/19	..	40	2.0	...	1.7	.....	0	0	1	0	0	0
2/20	..	..	...	...	....	Brown	...	0	0	0	0	1
2/25	60	46	1.4	...	3.7	Dark brown	+	+	0	0	0	0
3/ 3	75	63	2.8	0	4.8	Very dark	+	+	0	0	0	0
3/ 8	..	..	...	...	8.0	.....	+	+	0	0	0	0
3/10	..	35	2.0	...	1.4	.....	...	...	...	...	...	...
3/14	..	17	1.5	...	....	Normal	...	...	...	...	...	...
3/17	..	..	...	...	0.13	.....	0	0	0	0	0	0
1926 1/ 7*	50	..	...	...	0.8	.....	...	...	0	0	0	0

* Course of phenylhydrazine (total of 4.5 Gm.) during June, 1925.

Treatment.—A total dose of 4.5 Gm. of phenylhydrazine was given over a period of eight days. The total blood volume became reduced to 6,800 cc. (93 cc. for each kilogram of body weight), and the hemoglobin to 11.6 Gm. per cent. The number of erythrocytes fell to 2,730,000, and the leukocytes rose to 15,600. There was an increase of serum bilirubin to 4.8 Gm. during the peak of blood destruction; slight jaundice appeared but no severe hemolytic crisis occurred. No change in hepatic function was demonstrated by the dye test. Further destruction of the cells continued for six days after the cessation of treatment, the blood dropping to 6.5 Gm. of hemoglobin per cent, and the erythrocytes to 2,020,000. Moderate leukocytosis continued, the leukocyte count varying from 11,000 to 13,300. Regeneration of the blood began ten days afterward. At the time of dismissal the patient was much improved. Six months later there was a slight return of symptoms and he then took a subsequent course of 4.5 Gm. of phenylhydrazine hydrochloride. The effect of this course of treatment was not so marked, although relief from symptoms was complete. The patient returned to the clinic six months later, one year after his first admission. At this time his hemoglobin was 21.4 Gm. per cent. The erythrocytes numbered 5,520,000, and the leukocytes 9,600. The total blood volume was 9,330 (129 cc. for each kilogram

of body weight); the relative viscosity was 10.6. The platelets were slightly increased in number; the renal function was 50 per cent, and the serum bilirubin was 0.8 mg. There had been no weakness of the legs, and the man was able to carry on his work as well-driller without undue fatigue. His facial color was distinctly red; the skin capillaries showed the usual engorgement of the venous segment, and there was a marked increase in the number of visible capillaries. A third course of 4.5 Gm. of phenylhydrazine was given with satisfactory result (tables 13 and 14).

The volume of the whole blood was not high in this case, and some of the symptoms were apparently due to endarteritis obliterans. Distress and weakness in the legs were complained of rather than actual pain, but these symptoms disappeared with treatment and reduction in the volume of the blood.

SUMMARY AND COMMENT

Phenylhydrazine, first used in the production of experimental anemia in animals, has been administered to patients with polycythemia vera because of its specific effect in the destruction of erythrocytes. Given

TABLE 15.—*Average Amount of Hemoglobin Destroyed by Phenylhydrazine Hydrochloride*

Case	Weight, Kg.	Total Circulating Hemoglobin Destroyed, Gm.	Total Dose of Phenylhydrazine Hydrochloride, Gm.	Hemoglobin Destroyed,* Gm.
1	60	1,800	7.6	4
2	68	3,000	6.4	7
3	67	3,340	6.0	8
4	46	1,150	3.4	7
5	63	1,700	4.2	6
6	84	3,200	5.3	7
7	73	1,180	4.3	3
Average	65.8	2,200	5.7	6

* Calculated according to the Dye method on the basis of kilograms of body weight, by each gram of drug.

subcutaneously in animals it was shown to be very toxic, but given by mouth to patients its toxicity seems to be low. Recent experiments have also demonstrated that when the drug was given by mouth to the experimental animal, the toxicity was much lower. Acetyl phenylhydrazine is being used experimentally because of evidence which points to a still lower toxicity.

In the complete clinical and physiologic studies in seven cases of polycythemia vera treated by phenylhydrazine reported, the effect of phenylhydrazine on destruction of blood and the reduction of erythrocytes is definite, constant, and specific, and gives symptoms indicative of a hemolytic crisis. An increase in leukocytes is stimulated even by small doses of phenylhydrazine, and this stimulation is specific. The platelet count does not seem to be appreciably affected. The effect of the drug on destruction of blood was evident for from

seven to ten days after its discontinuance, and this observation should be taken into account in the practical use of the drug. The marked reduction in the volume of the blood and the symptomatic improvement accompanying it were most striking. The reduction in blood volume seemed to be directly proportional to the destruction of erythrocytes, and when anemia had been produced, a relative increase in the plasma volume was observed. Jaundice appeared early during treatment and was accompanied by an increase in the serum bilirubin. The bromsulphalein test showed no dye retention during treatment; the fructose tolerance test revealed no demonstrable change. The phenolsulphonphthalein test showed slight retention of the dye in three cases, although this may have been due to an inaccuracy caused by the dark urine; in instances in which the urine was cleared higher values were obtained. Chemical studies of the blood showed very marked elevation of the blood urea and slight elevation of the creatinine during treatment. The blood urea curve, however, followed the course of destruction of blood and was evidently due chiefly to the excessive destruction of cells rather than to retention, although a certain degree of retention may have been caused by an excessive amount of hemoglobin and its derivatives, in the tubules of the kidney, as suggested by the findings of Baker and Dodds.[15] Thrombosis occurred during the period of active destruction of blood in three cases: in one it followed an intravenous injection, in one it occurred spontaneously in the superficial veins of the left leg, and in another symptoms somewhat suggestive of infarction of the spleen were present. Thrombosis is seen in cases of polycythemia vera when no treatment is being given; nevertheless its occurrence during treatment by phenylhydrazine demands further consideration. Specific bacterial infection at a time of decreased resistance and the liberation of an excess of thromboplastic material as a result of the destruction of erythrocytes and possibly platelets are factors to be studied.

Following treatment the clinical improvement was satisfactory in all but one case in which marked hypertension persisted. Vertigo, fulness of the head, neuralgia, weakness and mental irritability all disappeared. Patients who had had pain in the legs claimed complete relief. A gradual increase in the erythrocytes and volume of blood necessitated a second course of treatment, in from three to six months after the first course. As a rule, the dose effective at the time of the first treatment was equally effective in the recurrences. This was especially true in one case in which, during the third course of treatment, destruction of blood was apparently just as active as during the first course on the same dosage. One or two doses of the drug each week, or a short course each month,

15. Baker, S. L., and Dodds, E. C.: Obstruction of Renal Tubules During Excretion of Hemoglobin, Brit. J. Exper. Path. **6**:247-260 (Oct.) 1925.

may prove effective in maintaining an approximately normal condition. Our patients have been able to determine for themselves by their symptoms when further treatment was required.

Particular attention should be directed to the cases in which there was pain in the legs apparently due to calcification of the arteries. The excellent results in these cases suggest that the drug may be beneficial in cases of endarteritis obliterans without polycythemia.

The drug was given in doses of 0.10 Gm. three times a day; the total amount given varied from 3.4 to 7.6 Gm., the average total being 5.7 Gm. It was estimated that each gram of phenylhydrazine brought about the destruction of an average of 6 Gm. of hemoglobin. It has been found wise to discontinue the use of the drug when the erythrocytes drop to 4,500,000, and it is estimated that destruction of blood will continue for approximately a week longer.

Phenylhydrazine hydrochloride, in general, causes more consistent improvement in the symptoms and a more constant reduction in the blood volume than either radiotherapy or venesection. The questions involved in the occurrence of thrombosis during treatment and the ultimate toxicity of the drug, especially on the liver, can only be decided by more extended experience and more prolonged observation.

THE PATHOGENESIS OF LIPOID NEPHROSIS *

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I.

Lipoid nephrosis is a disease characterized by an insidious onset, a chronic course, edema, oliguria, albuminuria, changes in the protein and lipoids of the blood, and the deposit of lipoids in the kidney. It occurs alone, or in combination with diffuse glomerulonephritis, or with amyloid degeneration of the kidney.[1]

The disease thus characterized has gradually won for itself a place as a distinct clinical entity as a result of the work of numerous investigators during the last fifteen years. It is desirable to follow some of the steps in this development. The disease was formerly included under the term of chronic parenchymatous nephritis or the large white kidney. When one reads the description of chronic parenchymatous nephritis in Senator's [2] work on diseases of the kidneys, it is evident that under this term are included the diseases that we have at present learned to separate into lipoid nephrosis and some of the forms of chronic diffuse glomerulonephritis. For the purpose of separating the inflammatory diseases of the kidney from the purely degenerative, Müller [3] in 1905 proposed the term nephrosis for the latter. Such a separation was at that time a purely pathologic one and could not be carried through clinically.

In 1907 appeared Loehlein's [4] work on the inflammatory diseases of the kidney. It showed the unity of all forms of diffuse glomerulonephritis and demonstrated that the subacute, subchronic and chronic forms are the result of a previous acute diffuse nephritis. It showed also the dependence of the pathologic changes in the tubules on those of the glomeruli.

The disease known as chronic parenchymatous nephritis presented many clinical difficulties. At times it was accompanied by a tense hard pulse, an increase in blood pressure, and cardiac hypertrophy; at other times these were absent. A step forward was made when Munk [5]

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1. Elwyn, H.: Nephritis, New York, Macmillan Company, 1926, p. 186.

2. Senator, H.: Die Erkrankungen der Nieren, ed. 2, Vienna, A. Hölder, 1902, p. 248.

3. Müller, F.: Verhandlungen der Deutschen pathologischen Gesellschaft, Jena, G. Fischer, 1905, p. 64.

4. Loehlein, M.: Ueber die entzündlichen Veränderungen der Glomeruli bei menschlichen Nieren und ihre Bedeutung für die Nephritis, Arb. a. d. path. Inst. zu Leipzig, 1907.

5. Munk, F.: Klinische Diagnostik degenerativer Nierenerkrankungen, Ztschr. f. klin. Med. **78:1**, 1913.

in 1913 attempted to separate clinically the degenerative diseases of the kidney. He found in some cases with marked albuminuria, edema and low blood pressure, the presence of double refractive lipoids in the urine and in the cells of the convoluted tubules of the kidney. In 1912-1914 Epstein [6] published studies on blood serums and edema fluids. He found in some cases of chronic parenchymatous nephritis a reduction in the total protein of the blood, and showed that this reduction is in the albumin fraction while the globulin is increased both relatively and absolutely. He also found that the edema fluid in this disease contained little protein, as low as 0.1 per cent.

In 1914 appeared the classical monograph of Volhard and Fahr.[7] These investigators showed that the pathologic changes in the various forms of glomerulonephritis can be correlated with the clinical phenomena. They also showed that of the degenerative changes in the tubules, for which the term nephrosis was used by Müller, one form, that of lipoid degeneration, corresponded to a definite clinical picture. Volhard gave a classical clinical description of this form which he called "genuine nephrosis" or chronic nephrosis. This form corresponds to the definition at the beginning of this article and has a clinical picture totally different from the other forms of tubular degeneration or nephrosis. It was necessary, if the term nephrosis was to remain generic for all forms of tubular degeneration, to have a special designation for the genuine nephrosis in which lipoid degeneration in the kidneys and lipoid changes in the blood are important features. Munk [8] proposed the term lipoid nephrosis. This term has been accepted by most writers on the subject.

Further advance in this disease was made by studies on the protein and cholesterin content of the blood; by studies on the basal metabolism; by the introduction of the high protein diet by Epstein [6] and of thyroid extract by Eppinger [9] in the therapy of this disease. Numerous case reports have appeared in the literature, so that at the present time the disease constitutes a distinct clinical and pathologic entity.

Of the numerous problems that call for solution in this disease, none is of such absorbing interest as that of the pathogenesis. Before discussing this, I shall review briefly the essential clinical features.

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6. Epstein, A. A.: Concerning the Causation of Edema in Chronic Parenchymatous Nephritis, Am. J. M. Sc. **154**:638 (Nov.) 1917.

7. Volhard and Fahr: Die Brightsche Nierenkrankheit, Berlin, Julius Springer, 1914.

8. Munk, F.: Die Nephrosen, Med. Klin. **12**:1019 (Sept. 24) 1916.

9. Eppinger, H.: Pathologie und Therapie des Ödems, Berlin, Julius Springer, 1917.

II.

The disease begins insidiously with loss of appetite, fatigue, pallor, and edema of the ankles. In some cases the onset is definitely dated from an attack of acute diffuse glomerulonephritis or from a pregnancy. Examination of the urine shows the presence of albumin. The other symptoms then make their appearance.

The urine is diminished in amount to as low as a few hundred cubic centimeters daily, for long periods of time. It contains large amounts of albumin, 5, 10 and 20 grams per liter; as much as 60 Gm. per liter has been recorded. The specific gravity is high and may reach 1.050. In the sediment are found hyaline and granular casts, leukocytes and epithelial cells, some of which contain lipoids. Doubly refractive lipoids are also found as free granules.

The edema appears first in the ankles or in the eyelids and spreads gradually. It involves the skin and subcutaneous tissue and follows the law of gravity, being found more in the dependent parts. The serous cavities are involved. The edema may involve the gastro-intestinal tract and cause diarrhea.

The blood changes affect the proteins and the lipoids. Myers [10] gives the following figures for the normal protein content of the blood: for the total serum protein, 6.5 to 8.2 per cent; for serum albumin, 4.6 to 6.7 per cent; serum globulin, 1.2 to 2.3 per cent. In lipoid nephrosis Epstein [11] found the figures for the total protein of the blood to average 3.928 per cent and the ratio of albumin to globulin to average 0.466 per cent of albumin to 3.426 per cent of globulin. Linder, Lundsgaard and Van Slyke [12] record the lowest figure for the protein in nephrosis as follows: albumin, 0.75 per cent; globulin, 2.84 per cent; total serum protein, 3.60 per cent. They conclude that the reduction is in the albumin fraction, and that the globulin is either normal or slightly increased. Fibrinogen was found to be increased by Kollert and Starlinger [13] and by others. The rate of sedimentation of red blood corpuscles is increased.

The cholesterin in the blood is increased. Normally it is 0.21 per cent, according to Bloor. In lipoid nephrosis figures as high as 1.3 per cent have been found by Epstein; up to 0.928 per cent by Schwarz and

10. Myers, V. C.: Chemical Changes in the Blood and Their Clinical Significance, Physiol. Rev. **4**:279 (April) 1924.

11. Epstein, A. A.: Further Observations on the Nature and Treatment of Chronic Nephrosis, Am. J. M. Sc. **163**:167 (Feb.) 1922.

12. Linder, G. C.; Lundsgaard, C., and Van Slyke, D. D.: The Concentration of the Plasma Proteins in Nephritis, J. Exper. Med. **39**:887 (June) 1924.

13. Kollert, V., and Starlinger, W.: Albuminurie und Bluteiweissbild, Ztschr. f. d. ges. exper. Med. **99**:426 (March) 1924.

Kohn;[14] up to 0.730 per cent by Hiller, Linder, Lundsgaard and Van Slyke.[15]

The blood volume is normal, which is of great significance. The total nonprotein nitrogen, urea, uric acid and creatinine are not increased in uncomplicated lipoid nephrosis. Figures slightly above normal occur, and such an increase is usually found when the edema fluid is quickly reabsorbed into the blood stream. When this occurs, the fluid entering the blood stream carried with it the nonprotein nitrogenous substances contained in the edema fluid, and thus helps to swell the total figure in the blood.

Tests for kidney function give a normal response provided the tendency to edema formation does not interfere with the tests. The basal metabolism has been found lowered in this disease by Epstein and Lande.[16] They report figures as low as minus 19 per cent.

An increase in blood pressure does not occur in pure lipoid nephrosis. The heart is not enlarged. On the contrary, it is often found on necropsy to be small and atrophic.

III.

When we look for the pathologic changes that underlie these clinical phenomena, we find comparatively little. In the case of an uncomplicated lipoid nephrosis we find in the kidneys lipoid infiltration in the cells of the convoluted tubules with a certain amount of hyaline degeneration; lipoid infiltration in the interstitial tissue of the kidneys, and moderate fatty degeneration of the glomeruli. It is this incongruence of the profound humoral changes with the comparatively slight anatomic findings which led many students of this disease to consider it the result of some general metabolic disorder. Munk[17] sees the essence of this disease in a physicochemical change involving all the colloids of the body. Similar views are expressed by others. Such general assumptions are, however, of little value.

The etiology of many cases of lipoid nephrosis is quite obscure. They come to the notice of the physician in an advanced state, and any exciting or predisposing factors cannot be determined. Others can, however, be definitely traced to an acute diffuse glomerulonephritis which preceded the onset of the symptoms peculiar to lipoid nephrosis. Occasionally one gets the opportunity of following a case from its beginning as an acute diffuse glomerulonephritis to the full development

14. Schwarz, H., and Kohn, J. L.: Studies of Nephritis in Children, Am. J. Dis. Child. **24**:125 (Aug.) 1922.

15. Hiller, A.; Linder, G. C.; Lundsgaard, C., and Van Slyke, D. D.: Fat Metabolism in Nephritis, J. Exper. Med. **39**:931 (June) 1924.

16. Epstein, A. A., and Lande, H.: Studies on Blood Lipoids, Arch. Int. Med. **30**:563 (Nov.) 1922.

17. Munk, F.: Pathologie und Klinik der Nierenerkrankungen, ed. 2, Berlin, Urban and Schwarzenberg, 1925, p. 298.

of lipoid nephrosis. Acute diffuse nephritis must, therefore, be considered as an etiologic factor. Lipoid nephrosis is also a frequent accompaniment of the subchronic and chronic forms of diffuse glomerulonephritis. The writers who assume that lipoid nephrosis is a purely metabolic disease consider the presence of a nephritis with the nephrosis as purely accidental. However, the combination of the two diseases is of such frequent occurrence that a closer relationship than accident must be granted.

Other diseases that seem to stand in some relationship to lipoid nephrosis are those which lead to amyloid changes in the organs, namely, tuberculosis, syphilis and chronic suppuration. Amyloid disease is frequently found combined with lipoid nephrosis.

Still problematic is the connection between pneumococcus infection and lipoid nephrosis. Since Volhard [18] first observed this, the termination of many of these cases by a pneumococcus peritonitis has been found to be a common occurrence. Such cases have been reported by Schwarz and Kohn,[14] Bock and Mayer,[19] Vandorfy,[20] Stolz,[21] Fanconi [22] and others. Stolz found in a case of nephrosis gram-positive diplococci in the walls of the glomerular capillaries, in the cells of the tubules, and in the intertubular capillaries. In another case he found pneumococci in the intertubular connective tissue and in the epithelial cells. Stolz is of the opinion that the pneumococcus there causes an inflammation that is at first acute, but soon takes on a chronic character, resulting in an injury to the tubules. At times the pneumococci invade the peritoneal cavity where, because of the presence of ascites, the serous cells have lost their bacteriocidal power. The repeated occurrence of pneumococcus peritonitis in these cases is certainly remarkable, and the possibility of this organism playing a rôle as an etiologic factor must be kept in mind. The organism may, however, be a secondary invader.

With these data in hand, how can we undertake the problem of the pathogenesis of this disease?

The essential elements that characterize lipoid nephrosis, aside from any negative features, such as the absence of hypertension, of cardiac hypertrophy, and of renal insufficiency, are: the albuminuria, the

18. Volhard, F.: Die doppelseitigen Hämatogenen Nierenerkrankungen, in Mohr and Staehelin's Handbuch der Inneren Medizin, Berlin, Julius Springer, 1918, **3**:1467.

19. Bock and Mayer: Ein Fall von genuiner Nephrose mit Pneumococcus Peritonitis als Ausgang, Med. Klin. **16**:101 (Jan. 29) 1920.

20. Vandorfy, J.: Ein mit Pneumococcus Peritonitis verlaufender Fall von Nephrose, Med. Klin. **17**:657 (May 29) 1921.

21. Stolz, E.: Ueber die sogennante Pneumokkokennephrose, Med. Klin. **18**:1376 (Oct. 22) 1922.

22. Fanconi, G.: Zur Oedemfrage; Genuine Nephrose und idiopathisches Oedem, Jahrb. f. Kinderh. **110**:12 (Sept.) 1925.

oliguria, the edema, the hypercholesterinemia, the changes in the plasma protein, the lipoid deposit in the cells of the convoluted tubules, and the lowered basal metabolism. Each one of these elements has been considered by some investigator as of central interest and importance. The disease occurs either alone or in combination with diffuse glomerulonephritis or with amyloid degeneration of the kidneys.

Do all these features appear at the same time, or does one symptom appear first and the others later? Are they all concomitant results of some unknown cause, or are some of the elements the result of others in this group? The correct answer to these questions is important. From those cases which come under observation when the disease is fully developed and which cannot be traced to a definite onset we are not able to learn that which will help us in answering the first of these questions. Occasionally, however, the opportunity is given to trace the symptoms to the time of onset, or more luckily still, to observe the patient from the beginning. I have had the opportunity to observe several cases from the onset of an acute diffuse glomerulonephritis. In these cases the symptoms of the acute nephritis, namely, the edema, hematuria, the increase in blood pressure, and the evidence of renal insufficiency soon disappeared, and only the albuminuria remained. The amount of albumin in the urine was large and within six months the other symptoms of lipoid nephrosis began to appear.

In the cases, therefore, which can be followed from an acute diffuse nephritis which had subsided, the first step in the development of the lipoid nephrosis is the persistent albuminuria. What is the cause of this persistence of the albuminuria?

The proteins in the urine have definitely been shown to be identical with the proteins of the blood, namely, serum-albumin and serum-globulin. According to the careful investigations of Csatary, cited by Senator,[23] the amount of globulin in the urine in parenchymatous nephritis is comparatively small and the albumin is present in many times the amount of the globulin. According to the recent investigations of Linder, Lundsgaard and Van Slyke [12] also, the albumin in the urine in lipoid nephrosis is present in many times the amount of the globulin. It is evident that the proteins of the blood, and especially the serum-albumin, escape into the urine. That they thus escape by way of the glomeruli can hardly be questioned. The evidence for this is presented by Cushny [24] and by Richards.[25] The reason for their escape in such large quantities without the presence of any inflammation in

23. Senator, H.: Die Erkankungen der Nieren, ed. 2, Vienna, A. Hölder, 1902, p. 262.

24. Cushny, A. R.: The Secretion of Urine, London, Longmans, Green & Co., 1917, p. 201.

25. Richards, A. N.: The Nature and Mode of Regulation of Glomerular Function, Am. J. M. Sc. **170**:781 (Dec.) 1925.

the glomeruli is not so obvious. In the presence of such an inflammation, the diminution in nutrition, especially in oxygen supply, to the glomerular and capsular epithelium results in the injury to the cells, which increases their permeability for the proteins of the blood. This injury usually persists in most cases for some time after the inflammation in the glomeruli has subsided, and the result is a persistent albuminuria for some period after recovery from an acute nephritis. It is evidently this damage which persists in an unusual degree in those cases which eventually progress to a lipoid nephrosis. Whether such cases of acute nephritis which subside and leave a persistent injury to the glomerular epithelium have the pneumococcus as the causative agent is a problem for future investigation.

The reason that the albumin escapes in larger quantities than the globulin is probably found in the fact that it consists of smaller molecular aggregates than the globulin. Cloetta [26] has shown that the relative amounts of albumin and globulin, which pass through a membrane, are dependent on the density of the membrane. The more dense the latter, the less globulin passes through. This fact is of importance for our further considerations.

We have, then, as the first step in the pathogenesis of lipoid nephrosis, the escape of the proteins of the blood plasma, especially the albumin, into the urine as a result of a previous acute diffuse glomerulonephritis which has subsided but has left a more or less persistent injury to the glomerular and capsular epithelium.

V.

Can we explain the other manifestations of lipoid nephrosis as a consequence of the loss of the proteins of the blood into the urine?

In the further considerations I shall take as a guide two principles that enter into the fundamentals of modern physiologic concepts.

1. The living organism continuously attempts to maintain normal values within narrow limits of variation for those substances which it needs in its economy and for those processes and activities within itself to which it has become adapted. The means that the organism uses in maintaining and regulating such values are only known in some instances, and then but incompletely. In cases in which the means are known it is evident that they are physicochemical, hormonal and nervous, with a center of control in the central nervous system. Examples are numerous, such as the maintenance and regulation of the acid-base balance, of the normal temperature, of the amount of sugar in the blood, of the rate of metabolism, and so on. The object of physiologic

26. Cloetta, M.: Ueber die Genese der Eiweisskörper bei der Albuminurie, Arch. f. exper. Path. u. Pharmakol. **42**:453 (June) 1899.

investigation is always to find all the means by which such regulation is effected.

2. When any loss occurs in such substances, or a disturbance in such processes or activities with a threatened change in normal values, all the means of regulation of which the organism is capable are brought into play in an attempt, whether successful or not, to maintain the normal values. Here again, examples are numerous, such as all the reactions of immunity, the healing of wounds and compensatory hypertrophy. The object of investigation in pathologic-physiologic changes is to find all the means that the organism uses in averting a threatened change, or in compensating for a change that actually has occurred.

The tendency to take these principles as a guide in the consideration of the more fundamental vegetative functions of the organism is illustrated in such discussions as that of Henderson [27] on the physiologic regulation of the acid-base balance; that of McLean [28] on edema, and that of Siebeck [29] on the fluid exchange.

With these principles in mind we may attempt to trace the consequences that follow the continuous loss of serum-protein, especially serum-albumin, by way of the urine. We shall attempt to view the essential elements of lipoid nephrosis as results of a disturbance in regulation, consequences of an attempt on the part of the organism to prevent the further loss of protein and to compensate for that which is already lost.

The amount of albumin lost in this manner may be very large. Senator [23] records a case in which the total amount of protein in the urine during one day was 22.4 Gm. He cites another case in which from 30 to 35 Gm. was found daily for several successive days. Epstein [9] observed an albuminuria of several months' duration with a daily output of protein ranging from 18.5 to 26.2 Gm. That the daily loss of such large quantities of serum-albumin must necessarily reduce the amount in the blood plasma is self-evident. This was known to the older writers who spoke of a hypalbuminosis, and it has been recently emphasized by Epstein. Evidently the loss of so much plasma protein is not easily made up, which explains the low figures for the albumin and the total protein in the blood in lipoid nephrosis. It does not explain the absolute increase in the globulin fraction.

How does the organism attempt to compensate for such a loss? An attempt to compensate must be assumed if we hold to the principles enunciated above. For it is evident that the constancy of the normal

27. Henderson, Y.: Physiological Regulation of the Acid-Base Balance of the Blood and Some Related Functions, Physiol. Rev. **5**:131 (April) 1925.

28. McLean, F. C.: Edema as a Problem in Physiological Regulation, Physiol. Rev. **5**:618 (Oct.) 1925.

29. Siebeck, R.: Physiologie des Wasserhaushaltes, in Handbuch der Normalen und Pathologischen Physiologie, Berlin, Julius Springer, 1926, **17**:161.

blood protein presupposes functions which though not fully understood, must evidently be maintained.

In reviewing the clinical features of lipoid nephrosis we find two elements that may be viewed in the light of an effort on the part of the organism to compensate for the loss of albumin and to prevent a greater loss. These are the increase in the plasma globulin and the diminution in the urinary output.

We have said previously that the globulin is increased not only relatively but also absolutely. This has been found by most investigators in this field. The globulin has a larger molecular aggregate and is lost in the urine in much smaller quantities than the albumin. Although it does not replace the entire amount of the lost albumin, yet we may well consider its increase as an attempt on the part of the organism to compensate for the loss of the albumin.

The diminution in the amount of urine may be viewed as an effort to prevent a greater loss of albumin by restricting the amount of fluid in which it escapes. The glomerular function that is responsible for the filtration of fluid is controlled by many factors, chemical, physical, hormonal, and from the central nervous system. It has been shown by Richards [25] and his associates that the number of glomeruli, and even the number of loops in an individual glomerulus, which are active at one time vary considerably, and can be made to vary by different means. In lipoid nephrosis we may, in the light of the above mentioned physiologic principles, consider the diminution in the urinary output as due to a smaller number of the glomeruli being active at one and the same time in an effort to lessen the loss of proteins from the blood.

We have then, as a second step in the pathogenesis of lipoid nephrosis, the effort on the part of the organism to restrict the loss of protein by diminishing the amount of urine; and to replace the lost albumin by an increase in the amount of the globulin, which is of a larger molecular aggregate, and which passes less easily through the injured glomerular filter.

VI.

We have so far discussed the albuminuria, the oliguria, and the changes in the protein of the blood. We come now to the consideration of the edema. The explanation for the edema in this disease has always been difficult, and numerous theories have been evolved. Most of these are unsatisfactory. Usually each investigator has attempted to explain the edema on the basis of some single physical or chemical factor. Recently, Loeb [30] and McLean [28] have reviewed the problem of edema from the point of view of the regulation of the bodily fluids in the economy of the organism, and especially from the point of view of the

30. Loeb, L.: Edema, Baltimore, Williams & Wilkins Company, 1923.

maintenance of the normal blood volume. In discussing the edema of acute diffuse glomerulonephritis elsewhere,[31] I maintained that the edema there is produced in an attempt on the part of the organism to get rid of the excess of fluid in the vascular system, and to maintain the normal blood volume.

The maintenance of the blood volume within normal variations is evidently of the utmost importance to the organism. It is seldom disturbed as numerous studies on blood volume have shown, and the means of its regulation are chemical, physical, hormonal, and by the central nervous system. In lipoid nephrosis the blood volume is normal, as has been shown by Linder, Lundsgaard, Van Slyke and Stillman.[32] Of the forces that are concerned in the exchange of fluids in the organism, McLean mentions diffusion pressure, hydrostatic pressure, osmotic pressure and difference in electrical potential; ionic equilibrium according to the Donnan formulation; the flow of lymph; the state of the capillary membrane.

In lipoid nephrosis the diminution in the amount of protein in the blood has been used to explain the formation of the edema. Epstein [6] assumes that "the loss of protein incurred by the blood serum through the continuous albuminuria causes a decrease in the osmotic pressure of the blood, which fact favors the absorption or imbition of fluid by the tissues." Schade and Claussen [33] designate the water-binding power of the blood proteins as the "oncotic pressure," which they do not consider to be the same as the osmotic pressure. Normally, this pressure averages 25 mm. of mercury, but in patients with renal edema the figures are below 20 mm. Both the osmotic and the "oncotic" pressures may well be among the forces that the organism utilizes in the regulation of the fluid exchange. They cannot, however, be the determining factors in the edema of lipoid nephrosis for at least two obvious reasons: first, variations in the extent of edema and even the absence of edema may be repeatedly observed in spite of low figures for the plasma protein; second, in spite of the low figures of the plasma protein which should lessen the entrance of fluid into the blood stream, the *normal blood volume* is maintained whatever the fluid intake might be, and whatever the variations in the extent of the edema.

I believe we must consider the problem of edema in lipoid nephrosis from the point of view of an effort on the part of the organism to maintain the normal blood volume. There are two gates through which

31. Elwyn, H.: Nephritis, New York, 1926, Macmillan Company, p. 110.

32. Linder, G. C.; Lundsgaard, C.; Van Slyke, D. D., and Stillman, E. G.: Changes in the Volume of Plasma and Absolute Amount of Plasma Proteins in Nephritis, J. Exper. Med. **39**:921 (June) 1924.

33. Schade, H., and Claussen, F.: Der onkotische Druck des Blutplasmas und die Entstehung der renal bedingten Oedeme, Ztschr. f. klin. Med. **100**:363 (May) 1924.

an excess of fluid in blood can be made to escape, by way of the kidneys, and into the tissues. By way of the kidneys the escape of fluid has become difficult because of the effort on the part of the organism to reduce the loss of albumin. It is obvious that with the normal intake of fluid there will soon be an excess which must be taken up by the tissues if the blood volume is to remain normal. In the actual formation of the edema, numerous factors are concerned which are at present not sufficiently understood.

We have now, as a further step in the pathogenesis of lipoid nephrosis, the formation of edema in an effort on the part of the organism to maintain the normal blood volume in spite of the reduction in the urinary output.

VII.

When edema occurs as a result of cardiac failure, or with an acute diffuse glomerulonephritis, a considerable amount of plasma proteins escapes into the edema fluid. This is not the case in the edema of lipoid nephrosis in which the fluid contains only about 0.1 per cent of proteins, or less. This prevention of the loss of blood protein into the edema fluid we must also consider as a part of the regulative mechanism for conserving the plasma protein. Evidently, instead of an increase in the permeability of the capillary wall, the permeability is lessened for the protein, so that water and salts only can pass through it. The mechanism by which this is effected we may conceive to lie in an *increased contraction of the capillaries*. We have some evidence for the presence of such a contraction in the marked pallor of these patients. This pallor is not due to anemia, for the red blood corpuscles and the hemoglobin are either normal in number and amount, or only moderately reduced. Krogh,[34] in discussing the contractility of the capillaries, cites Ebbecke "who points out the fact that redness or paleness of the human skin depends upon the quantity of blood present in the cutaneous capillaries and venules, that is, upon their state of dilatation or contraction."

A widespread contraction of the capillaries with a lessening of the amount of blood in them has as a consequence a diminution in the supply of nutrition and of oxygen to the tissues. This diminution in the nutrition causes a starvation of the tissues and organs, which is shown by the decrease in the basal metabolism, by the loss of flesh, by the lessened resistance to infection.

The diminution in the supply of oxygen results in a diminution of intracellular oxidation. Such a disturbance in intracellular oxidation Volhard [18] considers to be the cause of lipoid infiltration in the kidneys.

Whenever there is an inability on the part of the cells to utilize properly their nutritive supply, lipoids accumulate in the cells and then

34. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1922, p. 31.

appear in the blood. This is illustrated in the lipemia of diabetes. That a diminution in the oxidative ability causes the cells to take up lipoids is evident from the experiments of Chalatow.[35] He found that when the cells of the kidney tubules are poisoned by the administration of phosphorus, which inhibits oxidation, they easily take up cholesterin. The diminution in oxidation, due to the diminished blood supply to the tissues and organs as a result of capillary contraction, I consider to be the cause of the appearance of lipoids in the tissues and in the blood. By escaping through the glomerular filter the lipoids may also infiltrate the cells of the tubules, and they also appear in the urine.

I assume, therefore, that we have as a further step in the pathogenesis of lipoid nephrosis a widespread contraction of the capillaries as a result of an effort on the part of the organism to prevent the loss of plasma proteins by preventing their escape into the edema fluid. This capillary contraction results in a diminished content of blood in the capillaries as shown by the pallor of the patient. It results further in a diminished nutrition and diminished oxidation of the tissues and organs as shown by the lowered basal metabolism, the loss of flesh, and the lessened resistance to infection. The consequence of the diminished nutrition and oxidation of the tissues and organs is the appearance of lipoids in the cells, and as they accumulate they are washed into the blood stream, where their total amount is increased, as shown by the high figures for the cholesterin. The lipoids pass through the glomerular filter into the urine.

VIII.

We have used as a starting point for our comment the cases of lipoid nephrosis in which the development of the disease can be followed from the onset with an acute diffuse nephritis. In the cases in which the onset is not observed, but in which the symptoms can be traced back to an attack of acute nephritis that has subsided, the same manner of development may be assumed. In the course of chronic diffuse glomerulonephritis repeated attacks of acute nephritis occur, as I have pointed out elsewhere. Each of these acute attacks may then be considered as the starting point for the possible development of a lipoid nephrosis, which then accompanies the course of the chronic nephritis.

The cases that accompany amyloid degeneration have as their etiologic factors the diseases that are responsible for the deposit of amyloid, namely, tuberculosis, syphilis and chronic suppuration. In these diseases we must assume that their toxins injure the glomerular and capsular epithelium more or less persistently. This is then followed by albuminuria, and the continuous loss of large amounts of protein

35. Chalatow, S. S.: Die Anisotrope Verfettung im Lichte der Pathologie des Stoffwechels, Jena, G. Fischer, 1922, p. 117.

initiates the regulative and compensatory measures that result in the eventual development of the full clinical picture of lipoid nephrosis.

We thus have come to the conclusion that the first symptom of lipoid nephrosis is the result of an injury to the glomerular and capsular epithelium. This injury is the result of a previous acute diffuse glomerulonephritis, which has subsided, or of the toxins of chronic diseases, such as tuberculosis, syphilis and chronic suppuration. Such injury is present for a variable period in practically all cases of acute nephritis in which recovery has been made. This is evident from the persistence of a small amount of albumin in the urine for a variable period of time. Why such injury is more severe in some cases, resulting in the continuous loss of large amounts of plasma protein, is unanswerable at the present time. Perhaps such a severe injury occurs only in those cases in which the pneumococcus is responsible for the acute nephritis.

SUMMARY

1. The main features of lipoid nephrosis are: albuminuria, oliguria, edema, diminution in the total protein of the blood with a diminution in the albumin fraction and the relative and absolute increase in the globulin fraction, increase in the cholesterin of the blood, lowering of the basal metabolic rate, a practically protein-free edema fluid, and the deposit of lipoids in the cells of the kidney tubules.

2. The disease occurs either alone or in combination with diffuse glomerulonephritis or with amyloid disease.

3. The first symptom in the cases that can be observed from the beginning is the albuminuria.

4. The albuminuria is the result of a more or less persistent injury to the glomerular and capsular epithelium by a previous acute diffuse nephritis that has subsided. When lipoid nephrosis accompanies amyloid degeneration the injury to the glomerular and capsular epithelium is caused by the toxins of the diseases that are responsible for the amyloid deposit.

5. The oliguria is the result of a regulative effort on the part of the organism to prevent the loss of protein.

6. The absolute increase of the globulin fraction in the blood is the result of a regulative effort on the part of the organism in an attempt to conserve the proteins of the blood by replacing the lost albumin with a protein of a larger molecular aggregate, hence one that passes less easily through the injured glomerular filter.

7. The edema is the result of a regulative effort on the part of the organism in an attempt to maintain the normal blood volume. Since one of the gates by which the excess of fluid is eliminated, namely, the

kidneys, is less active, there is danger that the fluid volume of the blood will be increased. This is obviated by the formation of edema.

8. To prevent the escape of the plasma protein into the edema fluid, the capillaries become less permeable by increased contraction. The result is pallor, and a diminution in the supply of nutrition and of oxygen to the tissues and organs.

9. This diminution results in a disturbance of intracellular oxidation and of the proper utilization of foodstuffs.

10. The result is a lowered metabolic rate, loss of flesh, and a diminished resistance to infection.

11. The diminution of the utilization of nutrition also results in an increase of lipoids in the cells, and later in the blood, with the production of a hypercholesterinemia.

12. The lipoids of the blood pass through the injured glomerular filter and from the filtrate add themselves to the lipoids already present in the cells of the kidney tubules. They also appear in the urine.

13. The main features of lipoid nephrosis are thus considered from the point of view of regulation in an effort on the part of the organism to compensate for the loss of protein and to prevent a greater loss.

14. The possibility that the pneumococcus may be a causative factor in the production of the acute nephritis that precedes the development of lipoid nephrosis must be considered. Its continued presence in the kidney, as found by Stolz, is possibly responsible for its occasional invasion of the peritoneal cavity, and the development of peritonitis.

EPIGASTRIC PULSATION

THE DIAGNOSIS OF THE ARRHYTHMIA CORDIS THROUGH THE EPIGASTRIOGRAM *

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Before discussing the diagnosis of arrhythmia cordis through the epigastriogram, I should like to describe briefly the study of the epigastric pulsation, which we have been investigating since the year before last.[1]

The movement of the heart can be recorded at the epigastric region directly under the processus xyphoideus of the individual not only with the visible or palpable epigastric pulsation, but also, by certain methods, without the pulsation. We have named this tracing "epigastriogram" or "epigastriocardiogram."

I first studied the analysis of the epigastriogram through simultaneous tracings with several polygrams, i. e., abdominal aorta, radial, carotid, apex beat, jugular, hepatic pulse and also esophagocardiogram. The analysis of the epigastriogram reveals the following components: the wave a due to the contraction of the right auricle; the wave s′ due to the vibration of the ventricular muscle in the beginning of the ventricular systole and then the systolic valley s; the wave d due to the ventricular diastole, and the wave c simultaneous with the pulsation of the abdominal aorta.

We studied the various forms of the epigastriograms in several diseases, especially in diseases with visible pulsations, for instance, pulmonary emphysema, beriberi, anemia, morbus basedowii and various valvular lesions of the heart and also in asthenic constitution, and classified them as shown in the figure 1.

Then I investigated the application of the epigastriogram in the diagnosis of irregular pulse.

THE DIAGNOSIS OF IRREGULAR PULSE BY THE EPIGASTRIOGRAM

The cause of waves a, c and d in the epigastriogram is somewhat different from that of waves a, c and v of the jugular vein. In the first place the wave a of the former has its origin in the direct influence of the right auricular contraction on the epigastrium, while the wave a of the latter is caused by the transmission of the increase of the pressure of the right auricle. Second, the wave c of the former is caused by the direct transmission of the pulsation of the underlying abdominal aorta,

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1. Fukui, N.: On the Epigastric Pulsation, Acta scholae med. univ. imp., Kioto **7**:41, 1924.

while that of the latter is assumed to be due to the carotid pulsation or again to have its origin in the shut impulse of the atrioventricular valve. Third, the wave d of the former is caused by the change of the position of the heart in the beginning of diastole and is sometimes followed by two or three little waves, while the wave v of the latter has relation to the systole and diastole of the ventricle.

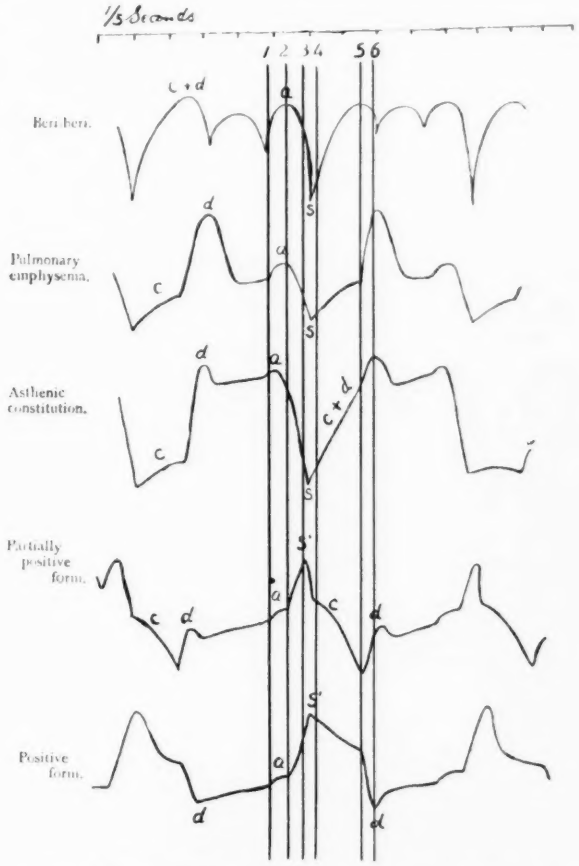
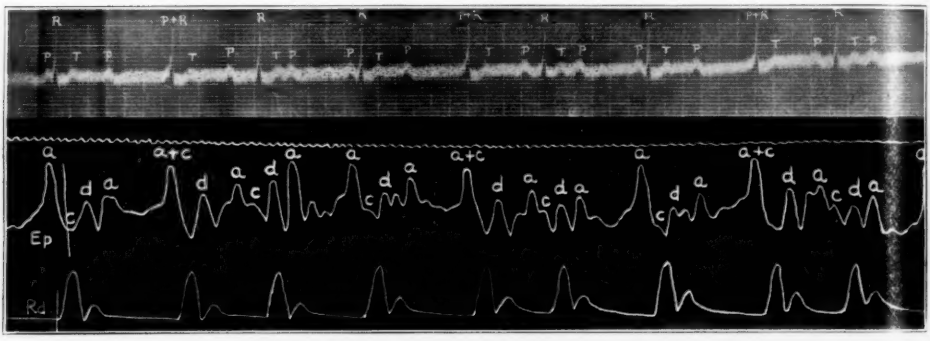


Fig. 1.—Several forms of epigastriograms: The perpendicular lines represent the time of the following events: (1) the beginning of the auricular systole; (2) the beginning of the ventricular systole; (3) the appearance of the pulse in the carotid; (4) the appearance of the pulse in the radial; (5) the closing of the semilunar valves, and (6) the opening of the tricuspid valves.

On the other hand, these waves of the epigastriogram can be regarded as similar in their nature to those of the jugular vein on account of the fact that the waves a both indicate the contraction of the right auricle

and the waves c both coincide with the arterial pulsation, though there is a minimal difference of time between the abdominal aorta and the carotid. This is the reason why we intended to substitute the epigastriogram for the venous pulse in the diagnosis of arrhythmia cordis. The recording of the jugular vein is difficult or often impossible, on account of the anatomic relationship of the regio colli. In my former report, the epigastriogram was compared with the venous pulse of the jugular vein in the diagnosis of the disturbance of atrioventricular conduction and of extrasystolic contraction and was assumed to be able to take the place of the venous pulse. In this article the epigastriogram is recorded simultaneously not merely with the jugular vein but also with the electrocardiogram, and the analysis of the epigastriogram and its clinical application are considered as to its correctness. Some cases of them will be reported as follows:


R
P+R
R
P+R
R
R
P+R
R
P
T
P
T
P
T

right heart represents always a high upheaval of the wave a, especially in a severe case. Vulvular failure also shows an epigastriogram similar to that of beriberi, when the right heart is dilated and hypertrophied as in the case of this patient. The jugular venous pulse indicates a very low wave (a) and the comparison of these waves (a) in the epigastriogram and the venous pulse is quite interesting. When the dilatation of the right heart of this patient was found by orthodiagraphy to have been reduced through treatment, the wave a of the epigastriogram became remarkably low and the form of the epigastriogram approached to the normal form, as is demonstrated in figure 3.

CASE 2.—*Parkinsonism and auricular extrasystole.*

The electrocardiogram of a man, aged 28, in figure 4 indicates the peak P, which often appears previous to the normal period. The time of the atrioventricular conduction is normal and P is regularly followed by R and T. The normal sinus irritation is not disturbed by the retrograde conduction of the stimulation of auricular extrasystole and thus the auricular extrasystole is followed by the normal sinus rhythm. The comparison of the epigastriogram with the electrocardiogram reveals the fact that the waves a, c and d coincide with the peaks P, R and T, respectively, and also that at the part where T is missing in the electrocardiogram, the wave d is reduced or missing in the epigastriogram.

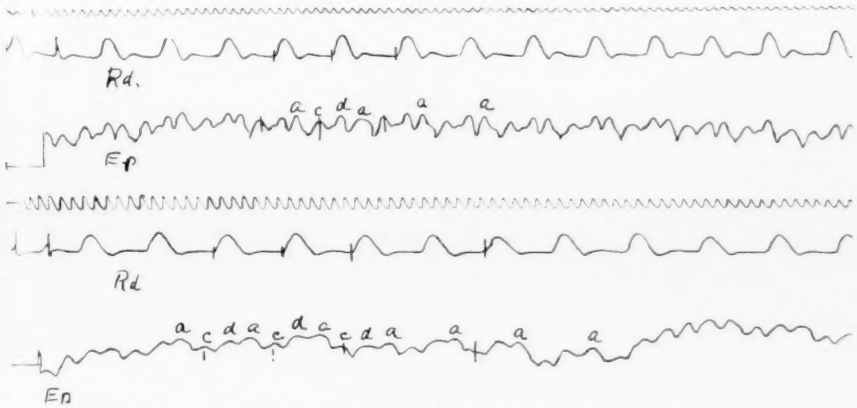


Fig. 3 (case 1).—Epigastriogram made when the hypertrophy and dilatation of the right heart was reduced through treatment, showing a remarkable lowering of the wave a as compared with that of figure 2.

The form of the epigastriogram of this patient indicates the form of the asthenic constitution. This patient has a paralytic chest and the limits of dulness and the sound of the heart are normal. The jugular vein represents the same diagnosis as the epigastriogram and electrocardiogram.

CASE 3.—*Mitral stenosis and insufficiency and auricular flattening.*

The electrocardiogram of a man, aged 23, in figure 5 shows a quite irregular feature and the auricular peak flattens with the frequency of about 250 times a minute. Now through comparison of the electrocardiogram and the epigastriogram it can be easily understood that the wave a of the latter flattens according to the flattening of the peak P of the former and in some intervals even the number of auricular flattening waves strictly coincide in both curves. On the contrary the jugular vein of this patient represents only the waves c and v, the wave a being missing in most parts.

The epigastriogram of this patient has a quite specific form, which is named positive epigastriogram. While the normal, i. e., negative epigastriogram consists of systolic retraction and diastolic swelling, the positive form swells in systole and retracts in diastole, so that the systolic valley of the negative form is trans-

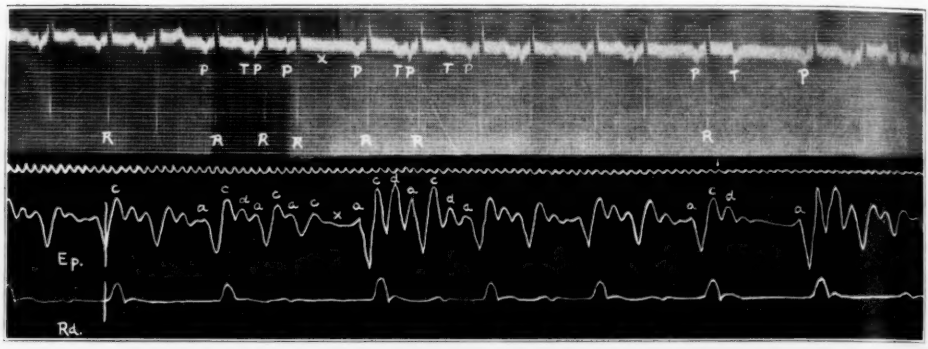


Fig. 4 (case 2).—Simultaneous electrocardiogram and epigastriogram and the radial record from a case of auricular extrasystole, showing the correspondence of the waves a, c and d, respectively, with the peaks P, R and T; especially where (x) the peak T is missing, there (x) is no wave (d). This epigastriogram reveals the asthenic constitution according to the classification of figure 1.

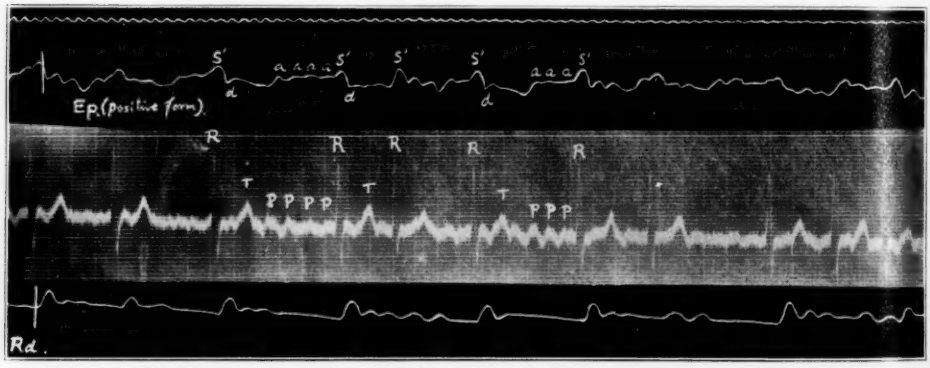


Fig. 5 (case 3).—Simultaneous electrocardiogram and epigastriogram and the radial record in auricular flattening, showing the synchrony of the flattening of the wave a and the peak P. This epigastriogram belongs to the positive form, according to the classification of figure 1.

formed into a peak (s'), in which the wave c is included, as if it lies in the depth of the valley s in the negative form. The contraction of the right auricle is expressed in most cases as the positive wave, but the negative wave a is not rarely recorded. Mackenzie[2] took the positive form of the epigastric pulsation

2. Mackenzie, J.: The Study of Pulse, 1902, p. 37.

for the sign of hypertrophy of the left heart, but his opinion is not always acceptable in view of my observation of many cases since the year before last, on account of the fact that the positive form is often recorded in the epigastric pulsation without hypertrophy of the left ventricle. As for this case, the heart is enlarged to the right and left and the apex beat is remarkably strong.

CASE 4.—*Contracted kidney and auricular fibrillation.*

In the electrocardiogram of a man, aged 68, in figure 6, P is missing and the interval is very irregular, while the relation between R and T is normal. The epigastriogram has the wave c and d, but no a and in some parts a slight prominence is seen which looks like wave a. This slight prominence s′ is named the partially positive form, which is shaped by the transformation of the forepart of the systolic valley into the positive wave as is shown in figure 1. This wave is often recorded in the subject with the heart intact and is sometimes mistaken for the wave a, because it appears directly after the auricular wave. The high prominence of the wave d in this epigastriogram is quite characteristic of pulmonary emphysema according to the classification of figure 1 and the epigastriogram of the aged is chiefly recorded in this type.

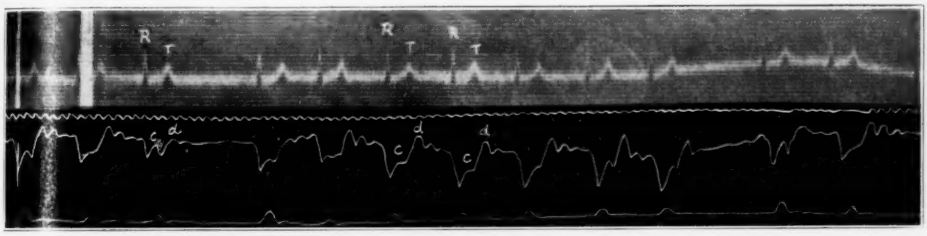


Fig. 6 (case 4).—Simultaneous electrocardiogram and epigastriogram and the radial record in auricular fibrillation, showing the defect of the wave a and the peak P, and in some part of the epigastriogram the partially positive wave s′ which looks like the wave a. This epigastriogram belongs to the form of pulmonary emphysema, according to the classification of figure 1.

SUMMARY

From the five cases mentioned, it can be easily understood that the peaks P, R and T of the electrocardiogram correspond minutely with the waves a, c and d, respectively, of the epigastriogram.

In the first place, from the comparison and analysis of the simultaneous tracings of the epigastriogram with several polygrams it was revealed that the wave a has its origin in the contraction of the right auricle, and this hypothesis that the wave a of the epigastriogram corresponds exactly with the peak P of the electrocardiogram in the former report gains confirmation through the results described here. The following facts are noteworthy: The wave a of the epigastriogram in figure 2, which represents the disturbance of atrioventricular conduction, coincides with the peak P of the electrocardiogram, and in figure 5 the wave a of the epigastriogram flattens in entire accordance with the flattening of the peak P of the electrocardiogram.

Second, it is evident that the wave c or the peak s′ of the epigastriogram is related to the ventricular contraction, because the wave c or the peak s′ corresponds entirely with the peak R of the electrocardiogram.

Third, though there is much discussion about the nature of the peak T of the electrocardiogram, it is quite interesting that the wave d of the epigastriogram coincides exactly with the peak T.

MYCOTIC ANEURYSM OF THE AORTA*

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AND
G. H. HANSMANN, M.D.
IOWA CITY

Mycotic aneurysms of the aorta occasionally develop during the course of intravascular infection. In most instances they are associated with a subacute bacterial endocarditis. They are usually small and rarely discovered until necropsy. This case is of interest because of the size and location of the aneurysm and the associated pathology.

REPORT OF CASE

History.—R. F., a boy, aged 17 years, was admitted to the University Hospital, Jan. 7, 1925. He complained of distress in the precordial region; pain in the left hip; weakness, and epistaxis. He stated that he had had measles and whooping cough in early childhood and rheumatic fever in 1919. After the latter illness the medical history was negative except for an occasional cold.

The present illness began in October, 1924, with fever, night sweats, loss of weight and frequent nosebleeds. He had had a daily afternoon temperature which usually reached 102 F. In November he was told by his family physician that he had heart trouble. The precordial pain was the chief complaint. It was very severe at times and aggravated by deep breathing. He had experienced, on a few occasions, severe pain in the upper left quadrant of the abdomen which appeared suddenly and in one instance lasted several hours. A few days prior to entering the hospital the left hip became sore and painful. He had lost 15 pounds (6.8 Kg.) in weight and felt weak.

Physical Examination.—The patient was slender, pale and poorly nourished. A petechial hemorrhage was discovered in the conjunctiva of the right eye. Others were seen in the axilla and on the abdomen. There was a generalized adenopathy. The glands were firm and varied from pea to hazelnut size. The lungs were negative. A prolonged systolic murmur was heard over the left chest, posteriorly. The cardiac impulse was diffuse and extended slightly outside the midclavicular line in the fifth interspace. A diastolic shock was felt over the entire precordia and there was a suggestive thrill. A systolic murmur was heard at the apex. It was even louder in the axillae and had a whistling quality. This was apparently the same murmur heard over the back. The second sound at the base was markedly accentuated. It was loudest to the right of the sternum and ringing in character. A diastolic murmur was heard in the second left interspace. The pulse was quick, but not distinctly water-hammer in character. The systolic blood pressure was 120 and the diastolic 60 mm. of mercury. The spleen was palpated and tender on pressure. The left hip was tender and painful on motion. The temperature, pulse and respiration were 101, 104 and 28, respectively. The red blood cell count was 3,190,000; the white count 9,800, and hemoglobin 46 per cent. In the differential count there were 83 per cent polymorphonuclears; 15 per cent lymphocytes; 1 per cent large mononuclears, and 1 per cent basophils. There was a marked variation in the size and shape of the red blood cells. The urine continually showed albumin, hyaline and granular casts and pus cells. On a few occasions

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red blood cells were seen and the chemical test for hemoglobin was positive. *Streptococcus viridans* was isolated from the blood.

In the roentgenogram of the chest taken January 7 there was a large spherical shadow which seemed to be continuous with the upper left aspect of the heart (fig. 1). In the fluoroscope examination the mass could not be seperated from the heart and did not pulsate. January 9, a pleural friction rub was discovered to the left of the sternum in the third and fourth intercostal spaces. The following morning the friction rub was still present and the percussion note at the base of the left lung was impaired. The breathing sounds were distant and bronchial in character. During the meantime the pain in the precordium continued; the breathing was more difficult and the coughing had increased. A needle was introduced into the left pleural cavity and 250 cc. of bloody fluid was withdrawn. This fluid contained numerous red blood cells and only an occasional white blood

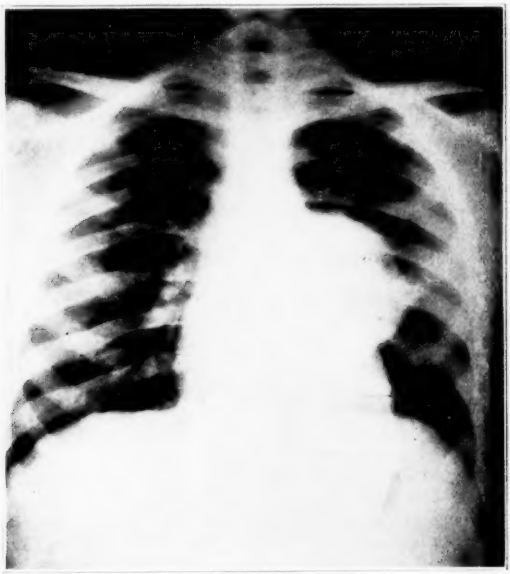

Fig. 1.—Jan. 7, 1925, aneurysm protruding into the left chest cavity.

cell. Cultures were made which remained sterile. During the night of January 16, the patient experienced severe pain in the precordial region which was aggravated by breathing and coughing. The signs of fluid in the left side of the chest increased. The roentgenogram (fig. 2) showed marked density of the entire left side of the chest and the heart and mediastinum seemed to be pushed to the right. Hereafter the course was rapidly downward and the patient died suddenly, January 28, following a short paroxysm of coughing. During the period of observation the temperature ranged from 98 to 104.

Necropsy Findings.—The body was poorly nourished and extremely pale. Petechial hemorrhages were seen in the conjunctiva, the axillae and on the chest. There was a large ecchymosis on the left hip. The peritoneal cavity contained 200 cc. of straw colored fluid. In the right pleural cavity a few fibrous adhesions were found. The left chest contained 2,000 cc. of recently coagulated blood. A

thick coat of fibrinous material was adherent to the left lung. The heart was in the normal position and weighed 370 Gm. The margin of the mitral valve was thickened and there were a few warty vegetations. There were only two aortic cusps and on each were recent fibrous vegetations which extended downward on the wall of the left ventricle. The muscle was pale and flabby. The aorta was mottled by the early lesions of arteriosclerosis. At the site of the opening of the ductus arteriosus during embryonic life, the aorta was constricted to less than half the normal size. A centimeter below this constriction, there was an opening into the wall of the aorta approximately 3 cm. in diameter. This opening connected with an aneurysmal sac 6 cm. in diameter which projected into the left chest (figs. 3 and 4). It was filled with an antemortem clot. The outer wall was composed of pleura and adventitia of the aorta. The remaining structure of the aorta had apparently been destroyed. The aneurysm had ruptured into the left chest cavity. Infarcts were found in the spleen and kidneys. There was a passive congestion of the liver and edema of the ankles.

Fig. 2.—Jan. 17, 1925, marked density of the entire left chest and the mediastinum; the heart is pushed to the right. The effusion was thought to have resulted from the slow leakage of blood into the left chest and mediastinum.

In the histologic examination, the aorta in the vicinity of the aneurysm was normal. At the base of the aneurysm, however, the wall was destroyed except for frayed out elastic fibers, among which streptococci were seen. The greater portion of the wall of the aneurysm was composed chiefly of an antemortem clot supported by fibrous connective tissue. The liver, kidney and heart showed focal areas of necrosis.

COMMENT

The case here reported had the typical clinical manifestations of a subacute bacterial endocarditis in which *Streptococcus viridans* was the responsible organism. Even though the course was rapid, the fatal termination was hastened by the rupture of a mycotic aneurysm.

The size and location of the mycotic aneurysm was unusual. In an extensive review of the literature, Stengel and Wolferth [1] were able to compile 213 cases and added four of their own. In sixty-six instances the aorta was involved, and a total of eighty-eight was found. The

Fig. 3.—Location of the aneurysm and site of the rupture.

aneurysms of the aorta were usually small and most frequently involved the root and ascending portion. Grant [2] has more recently made a careful study of the aortic lesions in thirty cases of subacute bacterial

1. Stengel, A., and Wolferth, C. C.: Mycotic (Bacterial) Aneurysms of Intravascular Origin, Arch. Int. Med. **31**:527 (April) 1923.

2. Grant, R. T.: The Aortic Lesions of Subacute Infective Endocarditis, Heart **11**:9 (Jan.) 1924.

endocarditis in some of which mycotic aneurysms were discovered. In all instances the lesions were found in the root or in the immediate vicinity of this section of the aorta. In one of the cases reported by Reifenstein [3] the aneurysm was located in the first portion of the descending aorta and in some respects resembled the present case in

Fig. 4.—Opening of the aneurysm into the aorta; constriction of the aorta at the upper level of the aneurysm.

that above the aneurysm in each instance there was a constriction of the aorta. In our case there were warty vegetations on the mitral valve which had been previously damaged by a rheumatic infection. More

3. Reifenstein, B. W.: Two Cases of Mycotic Aneurysm, Gonococcal and Pneumococcal in Origin, Am. J. M. Sc. **168**:381 (Sept.) 1924.

recently developed and extensive vegetations were seen on the aortic valves. In this connection it is to be recalled that there was a congenital absence of one aortic cusp. It is generally known that subacute bacterial endocarditis is often associated with congenital defects of the heart. In a series of thirty-one cases of subacute bacterial endocarditis studied by Lewis and Grant [4] 26 per cent had a congenital bicuspid condition of the aortic valves. They concluded that the congenital defect increased the susceptibility to the disease. It is possible that the impediment in the circulation induced by congenital defects is a factor contributing to the localization of the infection at these points. The constriction of the aorta in our case and the defect in the aorta reported by Reifenstein must have produced considerable interference with the flow of the blood. The configuration of the root of the aorta apparently favors the development of infection in this location. The involvement of this portion of the aorta in the absence of vegetations on the aortic cusps supports this conception.

The question of whether the mycotic aneurysm is produced by an infection of the intima or an infected embolus to the media by the vasavasorum is in dispute. The findings in the cases reported by Koritschoner [5] and Klotz [6] favor the latter conception. Furthermore, Quinby [7] and Dafoe [8] record instances in which mycotic aneurysms followed infection about the aorta. In the latter the aortic wall was invaded by an infection from adjacent tuberculous glands. In the study made by Grant, however, that portion of the aorta in which the intima was normal, the deeper layers, was free from inflammatory changes. He furthermore noted that the lesions in the aorta were very near the vegetations on the aortic valve or within the immediate vicinity. In the present case it is to be recalled that the aorta, up to the aneurysm, was normal. Should the damage have been produced by emboli to the vasavasorum, one would ordinarily expect to find a pathologic condition elsewhere in the media. It would thus seem that the evidence so far favors the intimal origin of mycotic aneurysm in the majority of instances.

Even though the pathologic findings in mycotic aneurysms are similar, a great variety of organisms have been identified in those

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4. Lewis, T., and Grant, R. T.: Observations Relating to Subacute Infective Endocarditis, Heart **10**:21 (April) 1923.

5. Koritschoner, R.: Beitrag. zur Kenntnis der mykotischen Aortitis, Centralbl. f. allg. Pathol. u. path. Anat. **23**:100, 1912.

6. Klotz, O.: Arterial Lesions Associated with Rheumatic Fever, J. Path. & Bacteriol. **18**:259, 1913.

7. Quinby, W. C.: Report of a Case of Infectious Aneurysm of the Aorta, Boston M. & S. J. **184**:14, 1921.

8. Dafoe, W. A.: Ruptured Aneurysm of Abdominal Aorta Due to Tuberculosis, Edinburgh M. J. **32**:291 (June) 1925.

instances in which the infectious agent was investigated. It is thus evident that the type of organism plays a minor rôle in the production of the mycotic aneurysm. In the present case *Streptococcus viridans* was responsible for the vascular injury. This organism is considered to be the least virulent of the streptococcus group and is thought by some to be incapable of producing a lesion unless there is a preexisting injury that favors its localization. In our case, however, there was an extensive destruction of the aortic wall and the aneurysm was as large as any heretofore reported. It would therefore seem that the cultural characteristic of the streptococcus on artificial mediums does not necessarily enable one to predict the type of lesion that they will produce in the living organism. The fact is not infrequently observed during postmortem examination and suggests that desirability of more precise biologic methods of studying the pathogenic organism.

In the present case the size and location of the aneurysm were such that it was possible to make a diagnosis before death. This type of aneurysm, however, is seldom recognized during life because of the small size and the frequent location in the root of the aorta. No doubt more would be diagnosed if the possibility was considered in every case of subacute bacterial endocarditis. They are apt to rupture and this feature should suggest the diagnosis. In our case the extensive deposit of fibrin on the lung and the infiltration of the mediastinum indicated that there was probably a slight amount of blood escaping from the aneurysm for several days before the fatal hemorrhage.

THE PHARMACOLOGY AND THERAPEUTICS OF NOVASUROL *

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CHICAGO

Novasurol, mercuricoxyacetobarbital, contains 33.9 per cent of mercury and is prepared in a 10 per cent aqueous solution. It was introduced in 1917 as an antisyphilitic. Voigt [1] and Levy-Lenz [2] in 1920 summarized its effect in syphilis. Compounds of mercury, principally calomel, have always ranked high among the diuretics. Increase in urination was early noted with novasurol, and in 1920 attention was called to this effect by Saxl and Heilig.[3] They found marked polyuria and a quantitative increase in the excretion of sodium chloride, both of which could be stopped by the use of atropine. They believed the effect was secondary to hydremia.

Brunn [4] in 1921 gave normal persons 1 or 2 liters of salt water before injection of novasurol, and obtained the same results as in cases of syphilitic myocarditis with decompensation, namely, great augmentation of the urinary total. At necropsy of the syphilitic cases, he noted no renal lesions.

Nonnenbruch [5] in 1922 agreed with Saxl and Heilig that the action was extrarenal and due to the mobilizing of sodium chloride and water from the tissue spaces into the blood, with a secondary overflowing of these substances from the blood into the urine, and therefore to no selective action on the kidneys.

Bleyer [6] in 1922 thought the hydremia theory plausible, but was not satisfied with the proofs available. Bohn [7] in 1923 concluded novasurol worked extrarenally. Tezner [8] in 1923 obtained a more rapid absorption

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* From the department of medicine and the Otto Baer Fund for Clinical Research of the Michael Reese Hospital and the Nelson Morris Memorial Institute for Medical Research.

1. Voigt: Novasurol, Therap. Halbmonatsh. **34**:263 (May 1) 1920.
2. Levy-Lenz: Erfahrungen mit Novasurol, Therap. Halbmonatsh. **34**:388 (July 15) 1920.
3. Saxl, P., and Heilig, R.: Ueber die diuretische wirkung von Novasurol- und anderen Quecksilberinjektionen, Wien. klin. Wchnschr. **33**:943 (Oct. 21) 1920.
4. Brunn, F.: Zur Wirkung des Novasurols als Diuretikum, München. med. Wchnschr. **68**:1554 (Dec. 2) 1921.
5. Nonnenbruch, W.: Ueber die wirkung des Novasurols auf Blut und Diurese, München. med. Wchnschr. **68**:1282 (Oct. 7) 1921.
6. Bleyer, L.: Erfahrungen über die Novasuroldiurese, Klin. Wchnschr. **1**:1940 (Sept. 23) 1922.
7. Bohn, H.: Experimentelle Studien über die diuretische Wirkung des Novasurols, Klin. Wchnschr. **2**:352 (Feb. 19) 1923.
8. Tezner, O.: Zum Mechanismus der Novasurolwirkung, Med. Klin. **19**:788 (June 10) 1923.

of subcutaneously injected physiologic sodium chloride solution in children following novasurol, and therefore declared the mechanism outside the kidney. Fodor [9] in 1923 claimed that because atropine stops the diuresis of novasurol the chemical affects a brain center which controls the metabolism of water and sodium chloride. Schlayer [10] in 1922 and Schur [11] in 1923 maintained a direct renal hypothesis. Crawford and McIntosh [12] in 1925 combined several ideas as follows: (*a*) For the first three hours hydremia exists; (*b*) following that a concentration of the blood occurs, and (*c*) this, with direct renal stimulation, causes the later increased flow.

Many observers obtained diuresis in cardiac edema by giving novasurol either intramuscularly or intravenously every three or four days. In markedly decompensated persons, however, its action has been best induced when injected intravenously with strophanthin. The diuresis usually appears within two hours and extends over twelve hours, during which time the quantity may reach 2 or 3 liters. Bohn [13] in 1924, however, found that this increased urination may last twenty-four hours. As high as 2 or 3 pounds (0.9 or 1.4 Kg.) in weight may be lost in one day, and during prolonged administration as much as 20 or 30 pounds (9 or 13.6 Kg.). Clinically, great improvement and a gradual resumption of compensation in cardiac cases has accompanied the polyuria. The dyspnea, cyanosis, râles, edema and fluid in the abdomen, chest and extremities have cleared up.

Edema due to syphilitic, rheumatic or sclerotic heart valvular and muscular injury has been benefited. Novasurol has been resorted to only when digitalis, rest in bed and dietary measures have proved unsuccessful. In some cases with tense abdominal walls due to ascites, paracentesis was first necessary. The action has been best marked in cases of decompensation accompanied by high blood pressure and cyanosis. Inflammatory exudates, intrapleural and intraperitoneal, tuberculous and nontuberculous, ascites due to cirrhosis of the liver or carcinomatosis of the peritoneum may be alleviated but not cured. In renal edema, novasurol is a distinct menace and will increase kidney damage. In diabetes mellitus, Bohn [13] found a lowering of the blood sugar and a disappearance of the glycosuria. In syphilis, its use with arsphenamine as a mercurial has been accepted by many authorities.

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9. Fodor, E.: Ueber das Indikationsgebiet des Novasurols als Diuretikum, Med. Klin. **19**:684 (May 20) 1923.

10. Schlayer: Stauungsniere, essentielle Nierenschädigung und Novasurolanwendung, Med. Klin. **18**:1425 (Nov. 5) 1922.

11. Schur, H.: Klinisch-experimentelle Studien über Novasuroldiurese und Nierenfunktion, Wien. Arch. f. inn. Med. **6**:175, 1923.

12. Crawford, J. H., and McIntosh, J. F.: Use of Novasurol in Cardiac Edema, J. Clin. Investigation **1**:333 (April) 1925.

13. Bohn, H.: Fortgesetzte Studien über Novasurol, Deutsches Arch. f. klin. Med. **143**:225 (Dec.) 1923.

TABLE 1.—*Changes Following Novasurol*

Date	Blood: Novasurol, Cc.	Blood: Non-protein Nitrogen	Blood: Urea Nitrogen	Blood: Sugar	Blood: Bilirubin Direct	Blood: Bilirubin Indirect	Urine: Albumin	Urine: Casts	Urine: 7 a. m. to 7 p. m.	Urine: 7 p. m. to 7 a. m.	Fluid: Intake	Fluid: Output
Case 1. Mitral Insufficiency												
10/19/24	...	..	..	..	..	..	+++	Many	.....	.....	.....	.....
10/20/24	...	..	..	..	..	..	++	Many	.....	.....	810	.....
10/21/24*	0.5	..	..	..	..	..	++	.....	.....	.....	1,650	1,080
10/22/24	...	..	..	..	..	..	+	.....	.....	.....	1,070	1,140
10/23/24	0.5	..	..	..	..	..	+	.....	.....	.....	1,230	810
10/24/24	...	..	..	..	..	..	..	.....	.....	.....	1,050	960
10/25/24	1.0	..	..	..	..	..	++	.....	.....	.....	1,091	3,780
10/26/24	...	..	..	..	..	..	Trace	Few	.....	.....	1,470	1,380
10/27/24	1.0	..	..	..	..	..	Trace	.....	.....	.....	1,530	2,280
10/28/24	...	..	..	..	..	..	Trace	.....	.....	.....	1,410	1,920
10/29/24	1.0	..	..	..	..	..	Trace	.....	.....	.....	830	2,400
10/30/24	...	..	..	..	..	..	Trace	.....	.....	.....	1,230	1,020
10/31/24*	1.0	..	..	..	..	..	Ft. tr.	.....	.....	.....	1,290	2,220
11/ 1/24	...	..	..	..	..	..	.....	.....	.....	.....	1,500	1,260
11/ 2/24	1.0	..	..	..	..	..	Ft. tr.	Few	.....	.....	1,170	2,220
11/ 3/24	...	..	..	..	..	..	Trace	.....	.....	.....	1,500	1,620
11/ 4/24	1.0	..	..	..	..	..	.....	.....	.....	.....	930	2,220
11/ 5/24	...	..	..	..	..	..	+	Occas.	.....	.....	1,500	960
11/ 6/24	1.0	..	..	..	..	..	.....	.....	.....	.....	990	2,220
11/ 7/24	...	..	..	..	..	..	Trace	.....	.....	.....	1,344	1,320
11/ 8/24	1.0	..	..	..	..	..	.....	.....	.....	.....	1,155	3,360
11/ 9/24	...	..	..	..	..	..	.....	.....	.....	.....	1,184	1,200
11/10/24	1.0	..	..	..	..	..	Trace	.....	.....	.....	1,376	2,700
11/11/24*	...	..	..	..	..	..	.....	.....	.....	.....	1,500	1,380
11/12/24	1.0	..	..	..	..	..	.....	.....	.....	.....	1,536	1,440
11/13/24	...	..	..	..	..	..	Trace	Occas.	.....	.....	1,184	1,200
11/14/24	1.0	..	..	..	..	..	Trace	.....	.....	.....	1,500	1,680
11/15/24	...	..	..	..	..	..	Ft. tr.	.....	.....	.....	1,352	1,200
11/16/24	1.0	..	..	..	..	..	Trace	.....	.....	.....	1,376	2,400
11/17/24	...	..	..	..	..	..	Trace	.....	.....	.....	1,248	1,680
11/18/24	1.0	..	..	..	..	..	Trace	Occas.	.....	.....	1,500	1,980
11/19/24	...	..	..	..	..	..	.....	.....	.....	.....	896	1,320
11/20/24	1.0	..	..	..	..	..	.....	.....	.....	.....	1,500	1,440
11/21/24*	...	..	..	..	..	..	+	.....	.....	.....	1,000	660
11/22/24	1.0	..	..	..	..	..	.....	.....	.....	.....	1,216	1,260
11/23/24	...	..	..	..	..	..	.....	.....	.....	.....	896	960
11/24/24	1.0	..	..	..	..	..	.....	.....	.....	.....	1,450	780
11/25/24	...	..	..	..	..	..	.....	.....	.....	.....	1,500	660
11/26/24	...	..	..	..	..	..	.....	.....	.....	.....	1,504	1,260
Case 2. Aortic and Mitral Insufficiency												
12/23/24	...	..	..	..	..	..	+	0	246	286	1,500	532
12/24/24	1.0	44	28	89	+	+	Trace	0	470	552	1,020	1,022
12/25/24	...	..	..	..	..	..	+	0	190	845	1,800	1,035
12/26/24	...	..	..	..	..	..	++	Many	540	376	1,590	916
12/27/24	1.0	..	..	..	..	..	+	0	551	205	1,580	756
12/28/24	...	..	..	..	..	..	+	0	414	196	1,680	610
12/29/24	1.0	..	..	..	..	..	Trace	0	1,555	174	1,500	1,729
12/30/24	...	..	..	..	..	..	Trace	0	245	250	1,050	495
12/31/24	...	55	..	95	+	+	Trace	0	347	230	1,080	577
1/ 1/25	1.0	..	..	..	..	..	Trace	0	2,215	1,165	1,350	3,380
1/ 2/25	...	..	..	..	..	..	Trace	0	222	170	2,140	392
1/ 3/25	...	..	..	..	..	..	Trace	0	258	302	1,140	560
1/ 4/25	1.0	..	..	..	..	..	Trace	0	960	475	1,020	1,435
1/ 5/25	...	..	..	..	..	..	Trace	0	460	280	840	740
1/ 6/25	...	..	..	..	..	..	Trace	0	292	412	1,080	704
1/ 7/25	1.0	60	32	58	+	++	0	0	935	742	720	1,677
1/ 8/25	...	..	..	..	..	..	0	0	407	356	900	763
1/ 9/20	...	..	..	..	..	..	0	0	368	418	1,140	786
1/10/25	1.0	..	..	..	..	..	0	0	1,762	747	960	2,509
1/11/25	...	..	..	..	..	..	0	0	507	368	900	965
1/12/25	...	..	..	..	..	..	0	0	504	515	840	1,009
1/13/25	1.0	..	..	..	..	..	0	Few	1,527	649	1,260	2,176
1/14/26	...	..	..	..	..	..	Trace	Few	395	720	1,110	1,115
1/15/25	...	58	30	..	+	++	Trace	Many	242	487	900	729
1/16/25	1.0	..	..	..	..	..	Trace	Many	1,453	555	1,170	2,008
1/17/25	...	..	..	..	..	..	Trace	0	1,100	606	1,200	1,705
1/18/25	...	..	..	..	..	..	+	0	313	174	1,080	487
1/19/25	...	63	..	Trace	Neg.		Trace	0	562	746	1,410	1,308
Case 3. Cardiosclerosis and Arteriosclerosis †												
12/ 2/24	...	..	..	..	..	..	Ft. tr.	0	.....	.....	.....	400
12/ 3/24	0.5	48	24	..	0	++++	Ft. tr.	0	.....	.....	870	600
12/ 4/24	...	40	20	..	Trace	++++	Ft. tr.	0	.....	.....	1,260	180
12/ 5/24	1.0	..	..	..	..	.....	.....	0	.....	.....	960	1,920
12/ 6/24	...	..	..	..	..	..	Ft. tr.	0	.....	.....	1,312	1,120

* Weight: 10/21/24, 190 pounds (86.2 Kg.); 10/31/24, 173 pounds (78.5 Kg.); 11/11/24, 155.5 pounds (70.5 Kg.); 11/21/24, 151.5 pounds (68.7) Kg..

† Large share of output in fluid feces.

TABLE 1.—*Changes Following Novasurol—(Continued)*

Date	Blood: Novasurol, Cc.	Blood: Non-protein Nitrogen	Blood: Urea Nitrogen	Blood: Sugar	Blood: Bilirubin Direct	Blood: Bilirubin Indirect	Urine: Albumin	Urine: Casts	Urine: 7 a. m. to 7 p. m.	Urine: 7 p. m. to 7 a. m.	Fluid: Intake	Fluid: Output
12/ 7/24	1.0	..	..	..	..	..	.....	0	.....	.....	1,106	1,580
12/ 8/24	...	..	..	..	..	..	Ft. tr.	0	443	180	952	623
12/ 9/24	...	..	..	..	..	..	Ft. tr.	0	125	188	1,020	313
12/10/24	1.0	42	26	..	Trace	++++	Ft. tr.	0	690	505	930	1,195
12/11/24	...	..	..	..	..	..	Ft. tr.	0	305	285	1,020	500
12/12/24	...	..	..	..	..	..	0	0	310	450	1,184	760
12/13/24	1.0	..	..	..	..	..	0	0	520	524	1,020	1,150
12/14/24	...	..	..	..	..	..	Trace	0	410	220	916	630
12/15/24	...	..	..	..	..	..	0	0	180	162	864	342
12/16/24	1.0	41	22	..	Trace	+	0	0	330	270	780	600
12/17/24	...	..	..	..	..	..	0	0	130	230	.....	360
				Case 4. Diabetes Mellitus and Cardiosclerosis								
12/22/24	...	35	15	196	0	0	0	.....	930	525	1,446	1,455
12/ 2/24	...	..	..	..	..	..	0	.....	830	1,140	1,290	1,970
12/24/24	1.0	..	..	..	..	..	Trace	0	1,470	968	1,380	2,428
12/25/24	...	..	..	..	..	..	Trace	0	798	1,438	1,500	2,236
12/26/24	...	..	..	..	..	..	Ft. tr.	0	1,510	1,306	1,260	2,816
12/27/24	1.0	..	..	..	..	..	Ft. tr.	0	1,469	600	780	2,069
12/28/24	...	..	..	..	..	..	Ft. tr.	0	1362?		230	1,362
12/29/24	...	37	15	266	..	..	0	0	1,194	615	.....	1,809
	...	..	..	276	..	..	.....	.....	.....	.....	.....	.....
	...	..	..	258	..	..	.....	.....	.....	.....	.....	.....
12/30/24	1.0	..	..	238	0	Trace	+	0	1,245	680	.....	1,925
	...	..	..	204	..	..	.....	.....	.....	.....	.....	.....
	...	..	..	185	..	..	.....	.....	.....	.....	.....	.....
				Case 5. Aortic Stenosis								
1/ 8/25	...	..	..	..	..	..	0	0	.....	80	900	.....
1/ 9/25	...	50	25	95	+	+	0	0	41	153	140	194
1/10/25	...	..	..	..	..	..	0	0	88	158	2,700	246
1/11/25	...	..	..	..	..	..	0	0	204	114	0	318
1/12/25	0.5	..	..	..	..	..	Trace	Many	233	84	900	317
1/13/25	...	..	..	..	..	..	Trace	Many	?	0	0	?
1/14/25	...	..	..	..	..	..	.....	Many	?	.....	90	?
1/15/25	0.5	..	..	..	..	..	..	Many	503		270	503
1/16/25	Patient died suddenly											
				Case 6. Hypertension and Chronic Nephritis								
3/15/25	...	..	..	..	..	..	++	.....	.....	.....	2,130	1,375
3/16/25	...	..	..	..	..	..	++	.....	.....	.....	1,890	1,885
3/17/25	0.2	100	..	111	..	..	+	Many	.....	.....	1,800	1,835
3/18/25	...	..	..	..	..	..	+	.....	.....	.....	1,800	2,331
3/19/25	...	..	..	..	..	..	+	.....	.....	.....	1,890	2,200
3/20/25	0.4	..	..	..	..	..	+	.....	.....	.....	1,800	2,440
3/21/25	...	..	..	..	..	..	+	.....	.....	.....	1,815	1,950
3/22/25	...	..	..	..	..	..	+	.....	.....	.....	1,800	2,670
3/23/25	0.6	50	..	91	..	..	Trace	.....	.....	.....	1,815	2,560
3/24/25	...	..	..	..	..	..	+	.....	.....	.....	1,830	2,530
3/25/25	...	..	..	..	..	..	+	.....	.....	.....	1,800	2,290
3/26/25	0.8	..	..	..	..	..	+	.....	.....	.....	1,860	2,240
3/27/25	...	..	..	..	..	..	++	Few	.....	.....	1,800	1,510
3/28/25	...	..	..	..	..	..	++	Few	.....	.....	1,830	1,500
3/29/25	1.0	..	..	..	..	..	+	Many	.....	.....	1,980	3,315
3/30/25	...	..	..	..	..	..	+	Many	.....	.....	1,950	810
3/31/25	...	..	..	..	..	..	+	.....	.....	.....	.....	.....
4/ 3/25	Died in uremia											

The ill effects of novasurol are few but generally agreed on, namely, gingivitis, hemorrhagic benign colitis, and occasionally renal damage. Saline cathartics should not be administered with novasurol.

METHOD OF INVESTIGATION

Six cases of marked cardiac decompensation were studied. Salt was restricted to 2 or 3 Gm. daily. Fluid intake was limited and measured. The patients were given treatment of rest in bed, digitalization, and

restriction of fluids and salt before novasurol was begun. In some cases digitalis was continued with the novasurol. Fluid output, in urine and feces, was estimated in twelve hour periods. Albumin determinations and microscopic examinations were made of each specimen of urine. Each week, blood chemical studies, including nonprotein nitrogen, urea nitrogen, sugar, plasma proteins, both albumin and globulin, and van den Bergh bilirubin were made.

The novasurol [14] was injected before breakfast at 7 a. m. The interval in the early work was two days, but later three or four days. The dosage was small; in case 6 only 3 minims at first, gradually increased to 1 cc. The route of introduction was at first intramuscular, but later intravenous.

REPORT OF CASES

CASE 1.—J. L., a bartender, aged 51, had mitral insufficiency. On admission, his complaints were as follows: ascites, four weeks; swelling of feet, two weeks; dyspnea, tightness across the chest and decrease in urinary output for three days. His face was puffy and pasty. The left heart border extended to the anterior axillary line; the right heart border to outside the right sternal border. The heart tones were faint and indistinct. There were some dulness and suppressed breath sounds at the right base posteriorly and a few coarse râles at both bases. The abdominal wall and sacral regions pitted on pressure. The abdomen was tense, distended, dome shaped and dull to percussion. The liver edge, tender and

TABLE 2.—*Effects of Novasurol on Plasma Proteins in Case 2*

	Plasma Protein, per Cent	Albumin, per Cent	Globulin, per Cent	Ratio Albumin : Globulin
Before novasurol				
1/14/25, 7:00 a. m.	7.39	4.43	2.96	60 : 40
After novasurol				
1/14/25, 7:30 a. m.	6.55	4.26	2.29	65 : 35
9:00 a. m.	7.21	4.54	2.67	63 : 37
11:00 a. m.	6.82	4.64	2.08	68 : 32
1:00 p. m.	6.61	4.56	2.05	69 : 31
3:00 p. m.	6.86	5.28	1.58	77 : 23
5:00 p. m.	6.52	5.41	1.11	83 : 17
7:00 p. m.	7.57	4.69	2.88	62 : 38
1/15/25, 7:00 a. m.	9.05	8.15	0.90	90 : 10

smooth, could be palpated and percussed 6 cm. below the costal margin. His lower extremities were edematous almost up to the knees. The history was suggestive of syphilis, but the blood Wassermann reaction was negative. Under routine treatment, the urinary output reached 800 cc. daily; the stools were frequent and fluid. The anasarca decreased slightly, but persisted in the abdomen and ankles. Novasurol was tried intramuscularly, 0.5 cc. and later 1 cc. every other day. An abdominal paracentesis removed 1,200 cc. of clear ascitic fluid. The fluid output at once rose from 800 to 2,400 cc. daily, at first largely in the stools, but later only in the urine. Simultaneously the weight dropped from 190 to 153 pounds (86.2 to 69.4 Kg.), the dulness and distention of the abdomen, the fluid and râles at the bases, and the edema of the ankles disappeared.

CASE 2.—M. S., a salesman, aged 40, had rheumatic pancarditis, aortic and mitral insufficiency and auricular fibrillation. He complained of edema of the feet for six weeks; vertigo for three weeks, and insomnia for six days. He was

14. The novasurol used in this study was supplied by the Winthrop Chemical Company.

markedly cyanosed and dyspneic. The thyroid was slightly and diffusely enlarged. The left heart border reached the posterior axillary line, the right heart border the right sternal border. At the apex one heard a loud systolic, followed by a middiastolic murmur. The right posterior base was dull and presented many coarse moist râles. The liver edge was tender four fingers below the costal margin. Both flanks showed shifting dulness and the feet pitted on pressure. The blood pressure was 130 systolic, 75 diastolic. Digitalization did not remove the anasarca. Five hundred cubic centimeters of fluid was removed from the right chest and novasurol therapy begun intramuscularly, but no benefit followed. The novasurol was then administered intravenously and in one month the edema of the feet, the ascites and râles, the cyanosis and dyspnea had disappeared.

CASE 3.—J. C., a tailor, aged 62, had cardiosclerosis and arteriosclerosis. He complained of chest pain and dyspnea for four years, and swelling of the feet for four weeks. His color was subicteric. The heart borders were enlarged to the right and left, and the heart tones were faint. Over the right posterior base one noted flatness and diminished breath sounds. The liver edge was smooth and tender five fingers below the costal margin. Examination revealed edema up to the midthigh bilaterally and over the sacrum and slight dulness in the flanks. The blood pressure was 150 systolic, 94 diastolic. Under rest and digitalis he improved slightly. Novasurol, intravenously, caused diuresis and cleared up the cyanosis, dyspnea and retention of fluid.

TABLE 3.—*Effect of Novasurol on Blood Sugar and Glycosuria in Case 4*

	12/29/24	12/30/24	Remarks
8:00 a. m.	266 mg. per 100 cc.	238 mg. per 100 cc.	1 cc. of novasurol given
9:00 a. m.	276 mg. per 100 cc.	204 mg. per 100 cc.	at 8:05 a. m., 12/30/24
10:00 a. m.	258 mg. per 100 cc.	185 mg. per 100 cc.	
Glycosuria.....	9.0 Gm.	7.5 Gm.	

CASE 4.—B. Z., a man, aged 58, had diabetes mellitus, cardiosclerosis and arteriosclerosis. He complained of polyuria, polydypsia and polyphagia for five weeks; dyspnea, weakness, and edema of the feet for two weeks. His skin was dry and the body was emaciated. There was a slight diminution of breath sounds over the bases. The heart borders were within normal limits; the radial arteries were hard and tortuous. The liver could not be palpated. Slight puffiness was noted over the feet. On the entrance day he excreted 63 Gm. of glucose. Under a rigid diet and digitalis the edema did not disappear. After one injection of novasurol, good diuresis occurred, the blood sugar fell and the swelling of the feet disappeared.

CASE 5.—S. Z., a shoemaker, aged 52, had aortic stenosis, mitral stenosis and insufficiency. He complained of dyspnea, cough and swelling of the abdomen and lower extremities for one week. There was moderate cyanosis and dyspnea. Numerous moist râles were present over both bases. Cardiac examination showed both heart borders to be outside the normal limits and a rough systolic thrill and murmur over the aortic area transmitted to the neck. The pulses were rapid and irregular. The liver edge was 11 cm. below the costal margin. The blood pressure was 120 systolic, 85 diastolic. Usual treatment did not improve the condition. An intravenous small dose of novasurol did not produce increased urination and the edema became worse. Sudden death occurred four days later.

CASE 6.—O. S., a salesman, aged 35, had hereditary hypertension and chronic nephritis. He entered the hospital because of cough, dyspnea, nocturia, progressive swelling of the lower extremities and apparent gain in weight. A slight exophthalmos was noted. Both lung bases were dull on percussion. The heart was enlarged to the right and left, and a slight systolic murmur was heard at the base. The liver edge was tender and extended a hand's breadth below the costal margin. There was shifting dulness in the abdomen, edema over the

sacrum and extending up both lower extremities to midthigh. The anasarca decreased slightly under usual care until an attack of follicular tonsillitis with high fever occurred, accompanied by suppressed urination and a return of the fluid retention. Intravenous novasurol in small increasing doses caused excellent diuresis. The edema lessened again, but the stupor deepened gradually and the patient died.

RESULTS

I. *Changes in Body Weight.*—Clinical improvement and diuresis were always accompanied by loss in weight. In case 1, this amounted to 35 pounds (15.9 Kg.) in three weeks. In the other cases, the patients' conditions precluded keeping a definite record. Concomitant with the weight decrease, the patients became very thin, since the decompensation had caused not only edema but also real tissue damage. Simultaneously, the dyspnea, râles, hydrothorax, ascites and edema of the extremities, both of subcutaneous tissues and musculature, vanished. In some instances, the size of a leg decreased one-third in diameter.

II. *Blood Changes.*—(*a*) Nitrogenous Elements: In case 2, the nonprotein nitrogen and urea nitrogen rose from 44 and 28 mg. per hundred cubic centimeters, respectively, to 63 and 30 mg. in twenty-four days. In case 3, in thirteen days the nonprotein and urea nitrogen fell from 48 and 24 mg. per hundred cubic centimeters to 41 and 22 mg. In case 4, the nonprotein and urea nitrogen were practically unchanged at the end of a week. Patient 5, with signs of marked cardiac decompensation and nonprotein and urea nitrogen of 50 and 25 mg. per hundred cubic centimeters died at the end of one week. Case 6, with nonprotein nitrogen of 100 mg. per hundred cubic centimeters, presented a drop to 50 mg. per hundred cubic centimeters under cautious treatment, but coma deepened and the patient died.

The clinical results agree sufficiently with the forecast of the nitrogenous constituents of the blood to lead us to believe the latter are of some value. As Crawford and McIntosh [12] have asserted, novasurol may act chiefly through renal stimulation. Since it is a mercurial compound, it may cause renal damage, if not as novasurol, then in some other form of mercury produced in the metabolic processes. From the data obtained, we think novasurol is a renal irritant. It should be begun in low dosage, and with great caution if nitrogenous retention is evident, and should not be administered over long periods.

(*b*) Sugar: The blood sugar was not pathologically altered during use of novasurol. In case 2, the level was 89 mg. per hundred cubic centimeters at the beginning and 58 mg. at the end of fourteen days. In case 6, in seven days the blood glucose fell from 111 mg. per hundred cubic centimeters to 91 mg. Bohn [13] found that the hyperglycemia of diabetes is reduced by novasurol. To corroborate this, we studied case 4, one of diabetes mellitus, arteriosclerosis and moderate edema. We stopped insulin and allowed a full diet without sugar. In table 3, we

show the blood sugar at 8 a. m., 9 a. m. and 10 a. m., namely, 266, 276 and 258 mg. per hundred cubic centimeters, respectively. On the next day at 8 a. m. the blood sugar was 238 mg. Five minutes later 1 cc. of novasurol was given, and at 9 a. m. the blood glucose was 204 and at 10 a. m. 185 mg. The first day 9 Gm. and the second day 7.5 Gm. of sugar were excreted. The explanation of the discrepancy between blood sugar and urinary sugar is not easy. However, it seems to corroborate the early hydremia postulated by Crawford and McIntosh. The lowering of the blood sugar is more apparent than actual, as proved by the glycosuria of 9 Gm. the first day and 7.5 Gm. the second day. Novasurol probably does not aid in the utilization of available sugar.

(*c*) Bilirubin: As a further check on the toxicity of novasurol, we made determinations of bilirubin by the van den Bergh method. We have followed the interpretations of McNee.[15] In case 2, both the direct and indirect were positive at the beginning of treatment, denoting a damaged liver, here probably due to decompensation. During the prolonged administration of novasurol, the direct remained about the same, but the indirect became stronger, thus probably pointing to increased liver damage, this time due to the medication itself. This agrees with the fact that novasurol injures the kidney and raises the blood nitrogenous substances. Within three days after the disappearance of the edema and the cessation of novasurol, the direct became a trace and the indirect negative. In case 3, in which novasurol was prescribed for only fourteen days and the nonprotein nitrogen was low, both the direct and the indirect bilirubin decreased. In case 4, bilirubin study demonstrated novasurol as innocuous over a short period, corresponding in this respect with the results obtained from blood nitrogen determinations. In case 5, a positive direct and indirect bilirubin and high blood nitrogen estimation gave a poor prognosis. We conclude that novasurol in small quantities for short periods may aid the excretion of bilirubin in chronic passive congestion of the liver. However, in prolonged administration, novasurol may be toxic to the liver.

(*d*) Plasma Proteins: In table 2 are given the results of novasurol on plasma proteins and blood dilution in case 2. Normally, according to Naegeli,[16] plasma proteins comprise from 6 to 8 per cent of the blood by volume. Of this, about 60 per cent is serum albumin and 40 per cent serum globulin. Our results were obtained by the Pulfrich dipping refractometer and the Hess viscosimeter. The plasma proteins fell for the first six hours; a rise to normal in twelve hours followed, and a concentration much beyond the original point succeeded at twenty-four

15. McNee, J. W.: Jaundice; a Review of Recent Work, Quart. J. Med. **16**:390 (July) 1923.

16. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Leipzig, Veit & Co., 1924.

hours. The serum albumin, however, did not fall much, and at twenty-four hours its percentage was almost twice that before injection. However, the serum globulin dropped irregularly until at twenty-four hours its volume was only 0.9 per cent.

We have been led to the following explanation for this: At first, an actual dilution and increase of blood volume exists. In compensation, reserve tissue albumin passes into the blood to restore the normal viscosity and composition of the blood. If, as is claimed by some, albumin constitutes the embryonic and globulin, the mature blood proteins, albumin would be the reserve in such an emergency. At twelve hours fluid excretion practically balances blood dilution. Hence, although the total blood volume probably surpasses normal, the blood proteins are of normal percentage. After twenty-four hours, fluid excretion has further concentrated the blood and left the total blood proteins high and their relation to each other altered.

III. *Changes in Urine.*—(*a*) Volume: Urinary changes are most easily grasped by both clinician and patient. In case 1, an initial injection of 1 cc. caused a twenty-four hour urinary output of 3,780 cc. Each subsequent dose gave rise to an excretion of 2 or 3 liters until the edema disappeared. In case 2, intramuscular administrations were followed by only slight diuresis and slight decrease in anasarca. Therefore, 1 cc. intravenously was used; this led to an output of 3,380 cc. of urine. This result was attained in case 2 thereafter by the intravenous route. In the intervals, a normal excretion of from 600 to 1,000 cc. prevailed. In case 3, 1,500 cc., only a slight rise, was poured out, but with a clearing of the edema. In case 4, the twenty-four hour excretion after each injection was more than 2 liters and the increased flow lasted several days. In case 5, one of acute and severe decompensation, no increase in volume was noted. In case 6, we note a peculiar circumstance. Because of the uremia present when novasurol therapy was instituted, the dosage was first set very low, 0.2 cc., and gradually raised. The urinary output responded quickly and reached over 2 liters, where it persisted even on days between injection. The anasarca gradually lessened but the uremia simultaneously deepened and caused an abandonment of the treatment. This unusual combination of decreasing edema and ascending uremia doubtlessly can be attributed to the diuretic and toxic properties of novasurol.

The time and route of excretion of fluid is worthy of notice. In cases 2 and 4, the largest amount occurred in the first twelve hours. In case 3, the output was distributed over twenty-four hours, and in case 6 over several days. Our findings agree with those of Bohn [13] that the excretion is prolonged over twenty-four hours or more in weakened and senile persons.

The urine did not account for the total fluid loss in all cases. A large portion diluted the stools in the early administrations in several cases, such as cases 1 and 6. For this reason, warning against the use of novasurol in hemorrhagic colitis or the ingestion of magnesium sulphate simultaneously with novasurol injection has been sounded. Colonic changes serious enough to cause a cessation of therapy did not occur in this series.

(*b*) Albumin and Casts: In each case, urinary albumin and casts were determined daily. In case 1, the urine contained much albumin and many casts. During treatment, the albumin lessened to a trace and the casts to only a few. In case 2, a marked albuminuria cleared with compensation. However, later, as the blood nitrogen rose, albumin appeared. The casts followed a similar course. In case 3, albumin and casts were practically absent throughout. In case 4, no albumin was noted until after a week of treatment. In case 5, also, albumin and casts were found only after several treatments. In case 6, albumin and casts were numerous throughout the therapy. Thus, although the albuminuria and casts corresponded usually with other indexes, it is more accurate to judge the effects and toxicity of novasurol by the blood nitrogen, urinary output and clinical course.

COMMENT

Obviously, such a compound should be added to one's armamentarium to be invoked only with great caution. Apparently, all cases of cardiac decompensation except those complicated with severe renal infection or damage may be benefited by the judicious administration of this substance, intravenously or intramuscularly, 1 cc. twice weekly. Such therapy will bring out the optimum results, namely, a great outpouring of fluid for twelve, twenty-four or even forty-eight hours. The three or four day interval allows the kidney opportunity to recuperate from the stimulus of the medication. No other diuretic accomplishes as much in cardiac decompensation. However, because of its toxicity, novasurol should not be used until the usual measures, such as rest in bed, digitalis and restricted fluids, have been exhausted. We have proof that, if not properly controlled, it is injurious both to the kidney and liver. The blood nitrogen figures and bilirubin have both mounted with increasing toxemia, uremia and lessened output. Albumin and casts do not guide reliably in this instance because of the chronic passive congestion of the kidneys present.

We agree with Crawford and McIntosh [12] on the pharmacology of novasurol. The drug produces for the first few hours a dilution, and later a concentration, of the blood that reaches its peak in twenty-four hours. We make no attempt to determine why the original hydremia

occurs, nor can we draw any definite conclusions from the authors cited. The increase in blood volume causes the early diuresis. Later, the drug stimulates the kidney to produce the urinary increase. Again we have no definite proof, but the blood nitrogen changes point to a renal action. We agree with Bohn [13] that the hyperglycemia of diabetes may be reduced by novasurol, but we believe this to be due to hydremia and not to any shift in the availability of the blood sugar as with insulin.

SUMMARY

One cubic centimeter of novasurol intramuscularly or intravenously twice weekly in persistent cardiac edema will cause profuse diuresis.

The appearance of toxicity may be noted by bilirubin determinations.

Novasurol may cause renal damage and should not be used in the face of nitrogen retention and lessened urinary output.

Diuresis appears three hours after administration; it lasts twelve hours in young individuals, and twenty-four or forty-eight hours in elderly and weak individuals.

Novasurol may induce a decrease in anasarca and an increase in uremia simultaneously.

In some cases, novasurol may not cause diuresis, although not producing any renal damage.

THE BASAL METABOLIC RATE IN CASES OF CHRONIC CARDIAC DISEASE AND IN CASES OF HYPERTENSION *

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In 1916 Peabody, Meyer and DuBois [1] found that patients with compensated cardiac disease showed no increase in basal metabolism. Nine out of twelve cases with dyspnea showed elevations in heat production above normal. They used both direct and indirect calorimetry. The respiratory quotients were between 0.73 and 0.94. They considered the earlier work of others of questionable accuracy because the respiratory quotients were too low.

Peabody, Wentworth and Barker [2] in 1917 studied twenty-four cases of cardiac disease and used as an additional index the vital capacity. Their results indicated that the rise in heat production was related to the degree of cardiac insufficiency. In direct accord with these observations Aub and DuBois [3] reported the respiratory exchange to be increased in cases of hypertension with dyspnea.

The subsequent studies of Peabody, Wearn and Tompkins [4] on "irritable heart" in soldiers, and of Boothby and Sandiford [5] on a large series of various types of cardiac disease confirmed the view that cardiac disease per se does not alter the basal metabolism but that other factors, such as dyspnea, are responsible for the elevations in heat production.

Within the last two years several additional reports have appeared in the literature on the influence of certain cardiac disturbances on the basal metabolism. Dieuaide [6] described a case of paroxysmal tachycardia which showed an increase of 16.7 per cent during a paroxysm in which the patient was dyspneic. The basal metabolic rate was normal during

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* From the Division of Laboratories, Montefiore Hospital.

1. Peabody, F. W.; Meyer, A. L., and Du Bois, E. F.: The Basal Metabolism of Patients with Cardiac and Renal Disease, Arch. Int. Med. **17**:980 (June) 1916.

2. Peabody, F. W.; Wentworth, J. A., and Barker, B. I.: The Basal Metabolism and the Minute-Volume of the Respiration of Patients with Cardiac Disease, Arch. Int. Med. **20**:468 (Sept.) 1917.

3. Aub, J. C., and Du Bois, E. F.: The Respiratory Metabolism in Nephritis, Arch. Int. Med. **19**:865 (May) 1917.

4. Peabody, F. W.; Wearn, J. T., and Tompkins, E. H.: The Basal Metabolism in Cases of "Irritable Heart of Soldiers," M. Clin. N. Amer. **2**:507 (Sept.) 1918.

5. Boothby, W. M., and Sandiford, I.: Summary of the Basal Metabolism Data on 8,614 Subjects with Especial Reference to the Normal Standards for the Estimation of the Basal Metabolic Rate, J. Biol. Chem. **54**:783 (Dec.) 1922.

6. Dieuaide, F. R.: Observations on the Respiratory Gases in Ventricular Paroxysmal Tachycardia, Bull. Johns Hopkins Hosp. **35**:229 (Aug.) 1924.

the interval between attacks. The author believed the added work of the heart and respiratory organs was responsible for the augmented metabolism. He used the Tissot method.

Hamburger and Lev,[7] using the Benedict apparatus, made sixty-six metabolic rate determinations on seventeen patients with various types of cardiac disturbances. They found that during cardiac decompensation the basal metabolic rate varied from 11.8 to 112.7 per cent above normal. Fever and acidosis were not important influences. While they state that the increased muscular activity resulting from accelerated breathing and cardiac contractions may be responsible for the elevated metabolism they believe that the actual causes of increased basal metabolic rate in decompensated cases of organic heart disease are not known. In a second article [8] they assert that 75 per cent of the decompensated cases of organic cardiac disease show an increased basal metabolic rate of an average of 39 per cent above normal and that the metabolic rate approaches normal as compensation returns. They report a case of paroxysmal tachycardia in which they found the basal metabolic rate to be elevated 11.1 per cent during the paroxysm. At the same time there occurred tachypnea, which phenomenon alone in a normal person caused a rise of 17.5 per cent in the basal metabolic rate. In addition to the accepted causes for the increased heat production in cardiac decompensation, namely, overactivity of both respiratory and heart muscles, they express the belief that other factors may be responsible for the increased heat production in these cases. They suggest variations of thyroid function as one of these factors, and discuss the possibility of a "transient hyperthyroidism during decompensation or changes in the thyroid circulation from long standing congestion of the superior circulation."

It seemed of value, therefore, to reinvestigate the problem and in particular to determine the basal metabolic rate in organic heart disease and whether cardiac overactivity such as may occur in a heart compensating for an organic defect or maintaining an elevated vascular tension is accompanied by increased heat production.

We have studied the metabolic rates obtained under basal conditions in a series of forty-two cases of heart disease including twenty-two patients with valvular lesions, fifteen with hypertension and cardiac hypertrophy, two with congenital heart disease and three with functional tachycardias. A total of 104 metabolic rate determinations was made in these forty-two cases.

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7. Hamburger, W. W., and Lev, M. W.: Basal Metabolism in Organic Heart Disease with Decompensation; Preliminary Report, J. A. M. A. **84**:587 (Feb. 21) 1925.

8. Lev, M. W., and Hamburger, W. W.: Basal Metabolism in Organic Heart Disease, Am. Heart J. **1**:240 (Dec.) 1925.

EXPERIMENTAL RESULTS

The patients in the postabsorptive state were each brought from the ward to the metabolism room in a wheel chair, and were given a minimum of twenty minutes' rest before the test was commenced. The Tissot method was used in all instances. All the results reported represent the findings in at least two successive determinations. Checks were obtained in the analyses of the gases in each instance reported.

We have observed the presence of anxiety and apprehension more frequently among patients with heart disease than in any other class of patients, an experience noted by other workers in this field. It has been found that in persons who do not have heart disease anxiety, fear and worry may give abnormally high metabolic rates. This applies probably even more to patients with cardiac disease than to other groups of cases. Consequently, we have taken special pains to train our subjects by first permitting each to witness another patient being run for metabolism and later, if necessary, have run the cardiac patient once or, in some instances, twice before the actual basal metabolic rate was determined. By such means we have obtained some interesting data which will be referred to later in the article.

In the accompanying table we consider as normal all results between — 10 per cent and + 15 per cent. The respiratory quotient is given in each case.

The patients referred to in the table as having good cardiac reserve were up and about and able to exert themselves moderately without respiratory embarrassment. Those with fair cardiac reserve were comfortable at rest, but were dyspneic on moderate exertion. The patients with poor cardiac reserve usually had enlargement of the liver or slight edema. They were dyspneic on slight exertion but were comfortable while at rest in bed.

COMMENT

Of the forty-two patients studied the heat production was found to be definitely elevated above normal in three cases. These patients all had dyspnea or hyperpnea which, we believe, was responsible for the increased metabolism. However, the possible influence of apprehension in these cases must not be lost sight of. The following case is described to illustrate how the anxiety that cardiac patients sometimes encounter may elevate the metabolism:

A woman, aged 65, with chronic cardiovalvular disease, showed metabolic rates of + 37 per cent and + 30 per cent the first and second times, respectively, that such determinations were made. The third and fourth metabolic rates, however, were normal (+ 2 per cent). All four determinations were made within ten days. She stated that she felt nervous during the first two determinations (although there were no outward evidences of such a condition) but more at ease during the third and fourth.

Summary of Findings

Case	Age	Sex*	Clinical Diagnosis	Pulse Rate	Blood Pressure	Cardiac Reserve	Dyspnea	Respiratory Quotient	Basal Metabolic Rate	Number of Determinations	Remarks
1	34	♂	Chronic glomerular nephritis; hypertension; cardiac hypertrophy	82	230/110	Good	No	0.81	Normal	2	Nitrogen retention
2	36	♀	Chronic glomerular nephritis; hypertension; cardiac hypertrophy; aortic insufficiency	96	250/150	Fair	No	0.72	Normal	4	Nitrogen retention
3	48	♀	Hypertension; cardiac hypertrophy	120	190/110	Fair	No	0.80	Normal	2	
4	47	♀	Hypertension; cardiac hypertrophy	96	190/105	Fair	No	0.75	Normal	2	
5	56	♀	Chronic endocarditis; left hemiplegia; hypertension; cardiac hypertrophy	84	175/115	Fair	No	0.80	Normal	4	
6	60	♀	Mitral insufficiency; hypertension; cardiac hypertrophy	80	175/ 90	Good	No	0.81	Normal	2	Died of cerebral hemorrhage
7	66	♂	Hypertension; cardiac hypertrophy	90	260/140	Good	No	0.86	Normal	2	
8	52	♀	Hypertension; cardiac hypertrophy	82	230/120	Good	No	0.73	Normal	2	Died of cerebral hemorrhage
9	51	♂	Hypertension; premature contractions; cardiac hypertrophy	84	180/ 90	Good	No	0.82	Normal	2	
10	60	♀	Hypertension; cardiac hypertrophy	60	235/100	Good	No	0.80	Normal	2	
11	15	♀	Persistent tachycardia (functional ?)	140	135/ 75	Good	No	0.75	Normal	2	
12	12	♀	Persistent tachycardia (functional ?)	120	125/ 75	Good	No	0.81	Normal	2	
13	63	♀	Hypertension; mitral stenosis; cardiac hypertrophy; auricular fibrillation	90?	190/ 90	Poor	Slight	0.83	Normal	2	Emphysema
14	27	♂	Chronic cardiovalvular disease; aortic insufficiency	80	100/ 60	Good	No	0.76	Normal	2	
15	18	♂	Mitral insufficiency; cardiac hypertrophy	96	100/ 70	Fair	No	0.91	Normal	2	
16	26	♀	Chronic cardiovalvular disease; mitral stenosis; aortic insufficiency	120	160/ 90	Poor	No	0.85	Normal	4	Erythema nodosum; enlarged liver; no edema
17	20	♀	Aortic insufficiency; hypertension; cardiac hypertrophy	90	200/140	Good	No	0.82	Normal	2	
18	36	♀	Neurosis; cardiac hypertrophy; kyphoscoliosis	120	120/ 80	Fair	Slight	0.76	Normal	2	Persistent tachycardia
19	40	♀	Mitral stenosis; auricular fibrillation; cardiac hypertrophy	108	170/ 90	Fair	No	0.82	Normal	2	
20	24	♂	Mitral stenosis; cardiac hypertrophy	80	110/ 80	Good	No	0.82	Normal	2	
21	14	♀	Congenital heart disease; cardiac hypertrophy	110	135/ 80	Good	No	0.79	Normal	2	

22	65	♀	Chronic cardiovalvular disease; cardiac hypertrophy; hypertension	108	205/110	Poor	No	0.78	Normal	4	
23	22	♂	Congenital heart disease; cardiac hypertrophy	110	140/ 80	Good	No	0.75	Normal	2	
24	30	♂	Mitral insufficiency; mitral stenosis; tricuspid stenosis; auricular fibrillation	96?	140/75?	Poor	Slight	0.78	Normal	2	Enlarged liver; slight edema
25	61	♂	Hypertension; cardiac hypertrophy	84	150/ 90	Poor	Slight	0.80	Normal	8	Enlarged liver; slight edema
26	38	♀	Hypertension; gallop rhythm; cardiac hypertrophy	110	220/120	Very poor	Yes	0.81 0.84	+36% +40%	4	Enlarged liver; edema
27	46	♀	Mitral stenosis; auricular fibrillation; cardiac hypertrophy	110?	145/100?	Very poor	Yes	0.84 0.79	+49% +43%	2	Enlarged liver; edema; hyperpnea
28	30	♀	Mitral stenosis; auricular fibrillation; cardiac hypertrophy; hypertension	96?	170/100?	Poor	Slight	0.81	Normal	4	Enlarged liver
29	35	♀	Mitral stenosis; cardiac hypertrophy; auricular fibrillation	63?	140/ 80?	Poor	Slight	0.81	Normal	2	Enlarged liver; acidosis
30	52	♂	Mitral stenosis; cardiac hypertrophy; auricular fibrillation; hypertension	108?	190/100?	Poor	Slight	0.80	Normal	2	Enlarged liver
31	60	♀	Chronic cardiovalvular disease; cardiac hypertrophy	96	130/ 85	Fair	Slight	0.76	Normal	2	Enlarged liver
32	40	♀	Mitral stenosis; mitral insufficiency; cardiac hypertrophy; auricular fibrillation	90?	140/ 90?	Poor	No	0.86	Normal	2	
33	22	♀	Mitral stenosis; premature contractions; cardiac hypertrophy	110?	140/ 90?	Poor	Slight	0.79	Normal	4	
34	45	♀	Mitral stenosis; aortic insufficiency; auricular fibrillation; cardiac hypertrophy	90?	100/ 60?	Very poor	Yes	0.80 0.81	+29% +33%	2	Hydrothorax; edema
35	54	♂	Hypertension; cardiac hypertrophy; syphilis	106	225/130	Good	No	0.80	Normal	2	
36	14	♀	Mitral stenosis; mitral insufficiency; cardiac hypertrophy	78	135/ 75	Good	No	0.76	Normal	2	
37	53	♀	Hypertension; cardiac hypertrophy	88	230/130	Good	No	0.78	Normal	2	
38	50	♂	Aortic insufficiency; hypertension; hemiplegia	90	240/ 60	Fair	No	0.83	Normal	2	
39	49	♀	Hypertension; cardiac hypertrophy	80	240/130	Fair	No	0.81	Normal	2	
40	45	♀	Hypertension; cardiac hypertrophy	78	250/120	Good	No	0.79	Normal	2	
41	26	♀	Mitral stenosis; chronic hypertrophy	88	95/ 70	Fair	No	0.80	Normal	2	
42	53	♂	Hypertension; cardiac hypertrophy; left hemiplegia	70	180/100	Good	No	0.90	Normal	2	

* In this table, ♂ indicates male; ♀, female.

In the remaining thirty-nine cases, we found that organic heart disease unaccompanied by dyspnea at rest does not elevate the basal metabolism.

The metabolic results obtained in cardiac disease may in addition be higher than normal by reason of certain sources of error such as the condition of the patient at the time of the test and the method used for its determination. If a patient with reduced oxygen saturation of the arterial blood, which is frequently observed in cardiac disease with or without cyanosis, is suddenly given pure oxygen to breathe, his blood will absorb relatively excessive quantities of this gas. If an oxygen absorption method is used (Benedict apparatus) an untrue and high result will be obtained. Thus, it has been found by comparing results obtained with the Tissot spirometer and the Benedict apparatus that the closed circuit method gave higher readings than the Tissot in cases with "arterial anoxemia."[9] The possibility exists, therefore, that in at least some of the subjects in whom Hamburger and Lev obtained increased metabolic rates that could not be explained on the basis of dyspnea, there may have been a state of reduced oxygen saturation of the arterial blood at the time the tests were made. They used the Benedict apparatus. Had the open circuit or chamber methods been used these patients' metabolic rates might have fallen within normal limits. We believe these criticisms cast some doubt on the observations reported by Hamburger and Lev. At all events, it is essential that they be confirmed either with the Tissot spirometer or with a method of direct calorimetry before their findings can be considered of significance. As appears from the table, we have been unable to do so using the Tissot apparatus.

Our results are virtually the same as those reported by Peabody, DuBois and their associates. We find that the metabolic rates of persons with organic heart disease, including those with hypertension and cardiac hypertrophy, obtained under basal conditions, fall within the accepted normal limits. High readings are usually due to dyspnea.

We have observed increased basal metabolism in a series of patients with true hypertension (systolic and diastolic) who did not have exophthalmic goiter and who were not dyspneic at the time the metabolic rates were determined. These cases have been reported elsewhere.[10]

CONCLUSIONS

The basal metabolic rate in patients with organic heart disease is normal. High readings are usually due to dyspnea.

Cardiac overactivity such as occurs in a heart compensating for an organic heart defect or maintaining an elevated vascular tension does not detectably elevate the heat production.

9. King, J. T., Jr.: Basal Metabolism, Baltimore, Williams & Wilkins Co., 1924.

10. Boas, E. P., and Shapiro, S.: Diastolic Hypertension with Increased Basal Metabolic Rate, J. A. M. A. **84**:1558 (May 23) 1925.

THE USE OF SODOKU IN THE TREATMENT OF GENERAL PARALYSIS

A PRELIMINARY REPORT *

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This is a preliminary report of the use of sodoku in the treatment of general paralysis. The series consists of twelve paretic patients who were inoculated with *Spirochaeta morsus-muris,* the etiologic agent of sodoku. This work was undertaken in an attempt to improve on the malarial method which has been used for eight or nine years in the treatment of general paralysis. It therefore seems advisable to preface the report of our investigations with an account of the treatment of general paralysis by malaria and other febrile producing methods.

In 1917 von Jauregg [1] introduced the malarial method. Since that time it has been quite generally utilized in most of the countries of Europe and also in the United States, the results reported being extremely favorable. The method usually consists of inoculating a patient with malarial blood, which leads to the development of malarial paroxysms. The patient is generally allowed to have from eight to fifteen paroxysms, after which the malaria is cured by quinine. According to the recorded observations in a considerable number of general paralysis patients treated in this manner very good remissions have been obtained shortly after the course of malarial infection. The reports in the literature and our own experience would seem to show that this method does definitely modify the course of general paralysis in a considerable number of cases.

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* Sodoku is a synonym for rat bite fever.

* From the Boston Psychopathic Hospital, the Department of Tropical Medicine of the Harvard Medical School, and the Danvers State Hospital. Financial assistance was obtained from the Division of Mental Hygiene of the Massachusetts Department of Mental Diseases.

1. Von Jauregg, Wagner: Ueber die Einwirkung der Malaria auf die progressive Paralyse, Psychiat.-Neurol. Wchnschr. **20**:132 (Aug. 31) 1918.

The original employment of this treatment in the hands of von Jauregg was largely empirical, but was based particularly on his previous experience with the various methods of producing fever in general paralysis patients. In 1887 he published an article [2] in which he reviewed previous observations tending to show that febrile diseases occurring in general paralysis patients often changed the course of the disease. Observations of the beneficial effect of febrile diseases on various psychoses had been recorded from time to time from the period of Hippocrates and Galen. As a result of these observations, von Jauregg suggested that the inoculation of malaria might be a justifiable means of treating cases of general paralysis, but he did not begin the use of this method until thirty years later. As early as 1889 he used various methods [3] of producing fever in general paralysis patients such as by the inoculation of tuberculin, Besredka's typhoid culture, streptococcus and staphylococcus vaccines. He was convinced that these methods, especially the one in which tuberculin was employed, were of considerable value and was supported in his belief by several investigators, notably Pilcz.[4]

Other observations were added tending to show the value of the occurrence of fevers in the modification of syphilis of the nervous system. For instance, it was stated that in certain countries such as Indo-China,[5] where both syphilis and malaria are endemic, cases of paretic and tabetic neurosyphilis are quite rare. This lead to the hypothesis that the malarial infection somehow protects the central nervous system of the individual from invasion by *Spirochaeta pallida*. Mattauschek and Pilcz,[6] in the now classical analysis of the histories of 4,134 Austrian army officers who had become infected with syphilis, pointed out that the patients who developed an acute febrile disease, such as pneumonia, typhoid and the like, during the first year of syphilis, did not develop neurosyphilis in the later course of their lives. On the contrary, those patients who did develop neurosyphilis, practically without exception, did not have acute febrile diseases during the first year of syphilis.

2. Wagner, Julius: Ueber die Einwirkung fieberhafter Erkrankungen auf Psychosen, Jahrb. f. Psychiat. **7**:94, 1887.

3. Von Jauregg, Wagner: Ueber die Behandlung der progressiven Paralyse, Wien. med. Wchnschr. **59**:2124 (Sept. 11) 1909; Ueber die Behandlung der progressiven Paralyse mit Bakterientoxinen, Wien. klin. Wchnschr. **25**:61 (Jan. 4) 1912.

4. Pilcz, A.: Zur Prognose und Therapie der Paralysis progressive, Ztschr. f. d. ges. Neurol. u. Psychiat. **4**:457, 1911.

5. Bercovitz, N.: Neurosyphilis and Malaria in Hainan (China), letter to editor, J. A. M. A. **82**:1713 (May 24) 1924.

6. Mattauschek, E., and Pilcz, A.: Beitrag zur Lues-Paralyse-Frage, Ztschr. f. d. ges. Neurol. u. Psychiat. **8**:133, 1912; Zweite Mitteilung über 4, 134 katamnestisch verfolgte Fälle von luetischer Infection, Ztschr. f. d. ges. Neurol. u. Psychiat. **15**:608, 1913.

Fortified by these observations and previous experience with febrile producing methods, von Jauregg [1] in 1917 started treating cases of general paralysis by the inoculation of malaria.

If one accepts the conclusion that malaria does modify the course of general paralysis, it is desirable to have some explanation of the way this is brought about. We can only theorize as to the explanation of this effect and none of the theories are convincing. However, two hypotheses that have been suggested may be mentioned. One is that the repeated high temperature reactions produced by the malaria are lethal for the spirochete; [7] another, that immunity reactions produced by the acute disease are effective against the etiologic agent of general paralysis.[8]

The advantages of inoculating the parasite of malaria as a febrile producing method may be summarized as follows:

1. Frequent high temperatures are produced.
2. A great majority of people are susceptible to the disease.
3. The rises in temperature recur at short intervals.
4. The disease is readily controlled by quinine.

There are, however, a number of disadvantages to the use of malaria in treatment:

1. It is not practical to keep the living organism either in culture or in a laboratory animal but, on the contrary, the disease must be transmitted from patient to patient. This means, if one is to carry on the work, that one must always have available a patient carrying the plasmodia in his blood. In the communities where malaria is not endemic, this is only possible if one is treating a large group of patients and can keep the strain going continuously. This is a great disadvantage and means that the treatment may not be available in many communities.

2. Malaria causes severe reactions and leads to a certain mortality. Due to the destruction of red cells, a considerable degree of anemia is usual. Jaundice is not an infrequent complication.

3. There is the possibility of inoculating the estivo-autumnal form by accident and in association with the tertian parasite.

4. Under most circumstances it is necessary to carry on the inoculation from patient to patient, which means the carrying over of syphilitic blood.

5. Some patients are not susceptible to malaria; some have a limited number of paroxysms which then spontaneously cease.

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7. Weichbrodt, R., and Jahnel, F.: Einfluss hoher Körpertemperaturen auf die Spirochäten und Krankheitserscheinungen der Syphilis Tierexperiment, Deutsche med. Wchnschr. **45**:483 (May 1) 1919.

8. Plaut, F.: Neuere Probleme der Paralyse und Tabes-therapie, Deutsche med. Wchnschr. **45**:1321 (Nov. 27) 1919.

In order to improve on malarial treatment, Plaut [9] introduced the method of inoculating patients with relapsing fever, which is less severe in its effect on patients than is malaria, and as laboratory animals are susceptible to infection with the organisms causing the relapsing fevers, they can be always available. Plaut also suggests a theoretical advantage of employing relapsing fever in that the organism of this disease is much more nearly related to *Spirochaeta pallida* than is the plasmodium of malaria, thus offering more likelihood of effective immunity reactions. However, there also are great disadvantages in the use of relapsing fever. The paroxysms of fever are likely to be separated by many days or weeks, so that at the best the treatment must take a considerable period of time. Relapsing fever, which is a self-limited disease, not infrequently ends before many attacks of fever have occurred. Furthermore, in Plaut's own experience, arsphenamine, which is supposed to be a specific for this disease, apparently was without effect so that the cases had necessarily to run their course. This is a fundamental objection as at times it is apparently impossible to control the disease. Several attempts have been made in the United States to utilize relapsing fever in the treatment of general paralysis but no strains of sufficient virulence have been obtained. We have tried to increase the virulence of the strain at our disposal, but have not been successful and we have only succeeded in getting the patients to have two, three or four mild rises in temperature. We have therefore sought for another organism that would have as many of the favorable characteristics as possible and as few of the unfavorable.

Spirochaeta morsus-muris, the specific organism of sodoku, meets most requirements. Sodoku is a disease fairly well known in Japan and has been occasionally recognized in the United States, as well as in most other countries of the world. Infection is produced by the bite of a rat or several other animals infected with *Spirochaeta morsus-muris.*

The disease produces a number of symptoms suggestive of syphilis. At the locus of the rat bite in the course of from one to fifty days (average, from five to ten days) a sore, suggestive of a chancre, appears. This primary lesion is covered by a black or reddish purple scab and has an average diameter of 2.5 cm. A lymphangitis from the sore to the neighboring lymph glands occurs with redness and slight tenderness. The regional lymph glands, as well as some at a distance, become enlarged and tender. The spirochetosis becomes generalized as the organisms are carried into the blood stream. After from five to

9. Plaut, F., and Steiner, G.: Recurrensinfectionen bei Paralytikern, Ztschr. Neurol. u. Psychiat. Orig. **53**:103, 1920.

fifteen days fever occurs, and skin lesions of various types, quite similar to those which characterize the secondary period of syphilis, appear over various parts of the body, particularly the trunk. The temperature, which rises from 104 to 105.5 F. or higher, is of the intermittent type, dropping after a period of a few hours to normal. This rise and fall is repeated from time to time, often at daily or bidaily intervals. The disease is said to be self-limited, but often continues with febrile exacerbations for a period of several months. It does, however, quickly respond to arsphenamine. In the disease acquired from the rat, the mortality, even in the untreated cases, is small and, as noted, may be readily controlled by arsphenamine.

Though sodoku has been recognized for a long time as a clinical entity, it is only in recent years that the etiology of the disease has been revealed. Futaki and his collaborators [10] were the first to describe a spirochete. Before this, however, Hata [11] had surmised that the causative agent was a spirochete and had introduced arsphenamine with brilliant curative results. The work of the Japanese has been confirmed in various countries of the world. *Spirochaeta morsus-muris* is a short but rather thick spiral organism. The curves are sharp and very regular. The body of the organism terminates in a point at either end, from each of which typically rises one flagellum (fig. 1). The extraordinary rapidity of movement of this organism is due to the flagella. The accounts of the morphology of the spirochetes observed by various investigators differ considerably, particularly as to the average length and the average number of spirals per organism. The points of difference, however, are not of great importance, for it has been shown by Robertson [12] that the average length varies considerably from time to time in the same strain. *Spirochaeta morsus-muris* can be kept indefinitely in laboratory animals. Mice and rats, when infected, show no signs of illness but harbor the organism in the blood. Guinea-pigs show signs that are comparable to the disease as observed in human beings. Thus, there is a primary lesion at the site of inoculation, followed by enlargement of the inguinal lymphatic glands, and fever. Alopecia is always a marked late manifestation in guinea-pigs but has not been observed in man. Our strain also invariably causes inflammation and later induration of the scrotum or labia.

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10. Futaki, K.; Takaki, J.; Taniguchi, T., and Osumi, S.: The Cause of Rat Bite Fever, J. Exper. Med. **23**:249 (Feb.) 1916; Spirochaeta Morsus-Muris, N. Sp., the Cause of Rat Bite Fever, J. Exper. Med. **25**:53 (Jan.) 1917.

11. Hata, S.: Salvarsantherapie der Rattenbisskrankheit in Japan, München. med. Wchnschr. **59**:854, 1912.

12. Robertson, A.: Observations on the Causal Organism of Rat Bite Fever in Man, Ann. Trop. Med. **18**:157 (Aug.) 1924.

The strain of spirochetes used in these experiments was obtained by one of us (M. T.) in November, 1923,[13] from a typical case of rat bite fever in a baby. It has been maintained in experimental animals since that time. The pathogenicity for laboratory animals has been the subject of another article to be published.[14] The strain has been passed through two mice, two rabbits and four guinea-pigs, a total of eight passages spread over a period of twenty months. The virus was kept for eleven months in one of the mice.

The material used for human inoculations consisted of the citrated blood taken under aseptic precautions from the heart of an infected guinea-pig or rat. In every case the blood was previously examined by dark field for spirochetes and two mice and two guinea-pigs were inoculated immediately afterward with the material used for human inoculations. All the animals inoculated with the material used for the human experiments developed typical signs of experimental rat bite fever with spirochetes in their blood.

The clinical effects produced by *Spirochaeta morsus-muris* seem to us to offer more favorable and fewer unfavorable characteristics than does malaria. The organisms can be kept in a laboratory animal, available for inoculation at any time. The patient's reaction is less severe than it is with malaria, although a fair degree of fever is obtained. It is readily controlled by arsphenamine. There is evidence of the production of immune bodies which, at least from the theoretical standpoint, may be of some importance.

Because of the facts enumerated, it seemed to us advisable to use this method in the treatment of general paralysis. The first point to be determined was the possibility of artificial inoculation. In a preliminary study three general paralysis patients were inoculated intradermally. In each instance there was definite evidence of the development of sodoku. A detailed account of one of these cases is given here (case 1). The general course in these cases was much the same, although varying in certain details. In the course of from three to five days a redness and swelling occurred at the site of inoculation, which was followed by the formation of a chancre-like sore.

These inoculations were made on the anterior surface of the right thigh. The lymphatics leading from this point to the groin became reddened and moderately tender. The regional lymph glands became moderately enlarged, to the size of a pea, and slightly tender.

About three days after the development of the sore, attacks of fever occurred, the temperature rising to 102 to 104 or 105 F., remain-

13. Shattuck, G. C., and Theiler, M.: Rat Bite Disease in the United States with Report of a Case, Am. J. Trop. Med. **4**:453 (Sept.) 1924.

14. Theiler, M.: Experimental Rat Bite Fever, Am. J. Trop. Med., to be published.

ing up for a few hours to a couple of days and then descending. Subsequent rises occurred at varying intervals from a day to three or four days. A number of attacks of fever occurred during a period of weeks and then apparently the temperature ceased spontaneously, or was stopped by arsphenamine. This tendency for the fever to cease and then recur is suggestive of what occurs in malaria. In sodoku, during the period of the fever, the lymph glands in various portions of the body become enlarged. At the same time skin lesions appear.

The effect of arsphenamine on the disease is extremely striking. The clinical manifestations disappear with great rapidity. Thus, in the

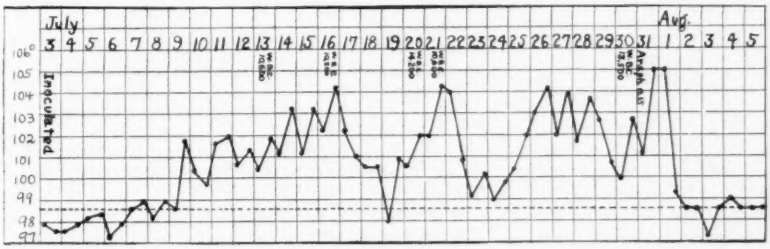

Chart 1 (case 1).—Temperature curve.

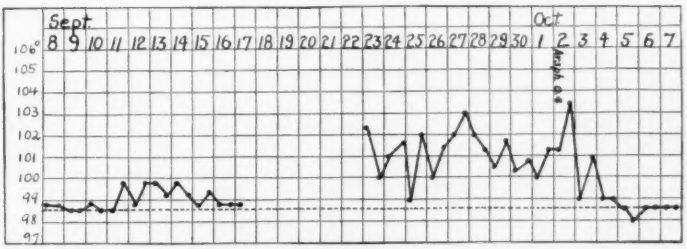

Chart 2 (case 1).—Temperature curve.

case of patient 1, 0.15 Gm. of arsphenamine produced what appeared to be a Herxheimer reaction or therapeutic shock followed by healing of the lesions. The temperature, which was about 101.5 F. at the time of the arsphenamine injection, rose to over 105 F. accompanied by a chill; the temperature then dropped to normal within several hours and there was no subsequent rise for some weeks (chart 1). The same therapeutic effect was obtained with each of the other patients. In the case of patient 1, two injections of 0.15 Gm. of arsphenamine were given and the clinical course closely observed. The temperature remained normal for fifty-two days and then again rose above normal (chart 2).

At the same time a localized lesion appeared. After ten days he was given another injection of arsphenamine and as on the previous administration of arsphenamine, the manifestations rapidly disappeared. Repeated injections were given and no further relapses have occurred although a period of several months has elapsed.

The other patients received a number of injections of arsphenamine and no true relapses occurred after treatment, although patient B developed some redness and tenderness at the point of the primary lesion during a short intermission of treatment.

The blood serum of these patients during the course of the disease and also subsequently to the apparent cure by arsphenamine contained immune bodies and rapidly killed in vitro *Spirochaeta morsus-muris*, thus indicating that the patients had not only been successfully inoculated, but had developed immune bodies which they carried in their blood for a long period.

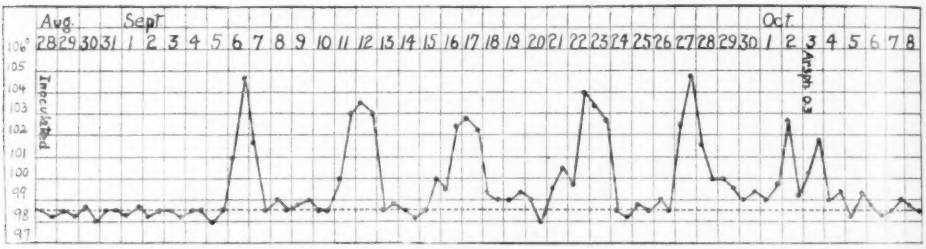

Chart 3 (case 2).—Temperature curve.

From these three cases we feel justified in drawing the following conclusions:

1. Sodoku can be artificially transmitted from animal to man.

2. The disease produces a generalized reaction with the production of fever and antibodies.

3. It is not dangerous to the life of the patient and is easily controlled by arsphenamine.

By intravenous inoculation, if care is taken not to allow the blood to get into the skin at the point of the venipuncture, no primary sore is produced. Eight patients were treated by intravenous inoculations. One patient died of general paralysis before the incubation period had passed. The remaining seven patients all showed clinical evidences of sodoku and the blood serum from each patient gave positive spirocheticidal tests. At the end of from one to three weeks fever occurs and later skin manifestations make their appearance (chart 3). There is, at times, a generalized glandular enlargement. The subsequent

course of the malady is much the same as that in which the inoculation is made intradermally. Infection produced by intravenous inoculation is controlled by arsphenamine just as promptly as when the infection is given intradermally. The amount of infective blood given intravenously varied from 0.1 to 1 cc. of rat or guinea-pig blood. There was no appreciable difference in the clinical course of the disease dependent on the amount of blood inoculated.

Sodoku was successfully produced in two patients subsequent to malaria. In one patient malaria was successfully transmitted after the patient had sodoku. In another patient an attack of relapsing fever was produced by injecting blood containing spirochetes of relapsing fever after the patient had had sodoku and still had immune bodies in his blood. This indicates that sodoku may be used before or after malaria, thus making it possible to use both methods in the treatment of a general paralysis patient.

REPORT OF CASES

CASE 1.—A., a white man, a dyer, aged 40, married, of German extraction, was admitted, June 6, 1925, because of confusion and disorientation. His past history was of no importance. His life was practically uneventful until suddenly in February, 1925, he had a "nervous breakdown." In June, he was not heard from for about a week until his wife received a call from the police. His brother secured his release by the police and had him sent to the Boston Psychopathic Hospital.

On admission the patient was overtalkative, easily distracted and grandiose. His pupils were sluggish; there were tremors of the tongue and slurring speech. His memory was poor, and he had ideas of grandeur pertaining to large amounts of money. The physical examination revealed signs characteristic of general paralysis, and the serology was strongly positive, showing the following: Wassermann reaction of serum, positive; Wassermann reaction of fluid, positive; cells, 48 per cmm.; globulin, 2 +; total protein, 70 mg. per hundred cubic centimeters; sugar, 55 mg. per hundred cubic centimeters; colloidal gold reaction, 5554420000. A diagnosis of general paralysis was made.

July 5, he was inoculated intradermally on the anterior surface of the right thigh under aseptic precautions with 1 cc. of citrated blood taken from a guinea-pig that presented typical signs of sodoku, and the blood of which revealed numerous spirochetes. From the same material, two guinea-pigs were inoculated immediately afterward, and in the course of time developed typical experimental rat bite fever with the causative organisms in the blood.

At the time of inoculation, the inguinal region revealed on examination a few small glands. The intradermal injection produced an indurated area about 3 cm. in diameter, without redness.

Three days later, the skin over the indurated area assumed a bluish color, involving an area 1 cm. in diameter. There was no temperature, and the glands remained unchanged. During the following two days the bluish tinge turned to a pink with redness surrounding it. Induration was present, and it was sore.

On the sixth day following inoculation, the temperature rose to 101.8 F. The patient complained of general malaise. The indurated area increased in size and became redder and more tender. The inguinal glands felt harder.

On the seventh day the temperature was still elevated. The glands were larger and harder. At the margin of the lesion a small bleb about 0.5 cm. in diameter appeared.

Later the patient complained of pain throughout the body, especially in his bones and joints, stating "it is just like the grippe." Several more blebs appeared around the primary lesion and the area of induration and redness became larger. The center of the lesion turned to a dark blue and broke down and exuded serum. The area of induration and inflammation increased in size rapidly, as did the glands. Smears were made from the exudation and were examined by dark field and stained with Giemsa stain but no spirochetes were seen.

On the twelfth day the glands became tender for the first time, although previous to this they were large and hard but not painful. The temperature rose to above 103 and the patient complained of general malaise again. The center of the inflamed area became gangrenous and formed a thick black eschar. Lymphangitis was present. The next day the temperature reached 104.4, and the white blood count was 10,200. Later, the temperature dropped to normal.

On the seventeenth day several small circular well defined elevated spots about 1 cm. in diameter appeared over the chest and left thigh. A gland puncture was performed and the substance was injected into two mice. The gangrenous portion began to separate from the healthy tissue and formed a round, well defined border. On the flexor surface of the left forearm a hard nodule presented itself, slightly red and tender. At this point venipuncture had been performed eight days before.

The following day many more spots appeared. The temperature rose to 104. The next day the temperature dropped, and the spots lost their deep rose color, became less defined, flattened out, and some had disappeared almost entirely. For the following day or so the temperature was normal and the spots were hardly discernible. Again the temperature rose and the spots reappeared, assuming a size, shape and appearance similar to those of the previous crop, but more spots appeared over the face, scalp, legs, abdomen and back.

On the twenty-eighth day the patient was given 0.15 Gm. of arsphenamine intravenously. In the evening the temperature rose to 105 and remained elevated until the following morning when it reached normal. During the height of the fever, the patient became delirious and excited and had to be kept in bed. This was similar to the so-called Herxheimer reaction or therapeutic shock as seen in the treatment of syphilis.

The day following the intravenous medication, the temperature became normal, the spots practically disappeared, and the ulcer revealed granulating tissue. At this time the serology was: Wassermann reaction of blood serum, positive; Wassermann reaction of spinal fluid, positive; globulin, 1 +; cells, 12 per cmm.; colloidal gold reaction, 3321000000.

Three days later the patient was given another dose of 0.15 Gm. of arsphenamine, and on the next day the plug of gangrenous tissue came away of its own accord and the red spots entirely disappeared, leaving an occasional desquamating area where a spot had been.

The next day the ulcer was perfectly clean and free of necrotic tissue. As the days went by the ulcer healed in a fairly rapid manner.

September 11, the patient complained of a head cold for which he was treated, and he apparently recovered. Four days later there appeared a small area of erythema on the lower eyelid in the same area where one of the characteristic red spots previously had appeared, and the left side of the nose swelled. The swelling extended to the left cheek and then to the glands at the angle of the jaw. The temperature ranged from 99 to 102 F.

Fifteen days following the first appearance of the swelling of the nose, the patient was given 0.2 Gm. sulpharsphenamine intravenously, and later 0.4 Gm. arsphenamine. Three-quarters of an hour after the second injection, he developed a chill lasting twenty-five minutes and the temperature rose to 102.2. Forty-eight hours later, the facial swelling and the enlarged glands had practically disappeared. Several days later he was working around the ward. He received subsequent weekly intravenous arsphenamine injections and there were no further relapses. The serology at this time revealed some improvement.

The patient was discharged from the hospital as improved and capable of taking care of himself. When last heard from, about five months later, no relapses had occurred.

CASE 2.—D., a white man, aged 34, married, an accountant, was admitted to the Boston Psychopathic Hospital, June 13, 1925, on the complaints of acting peculiarly, memory lapses, stammering speech, excitement and incoherence. The past history was of no importance. The onset of the illness was gradual, beginning with a physical decline in the spring of 1924. He became thin and was easily tired out; then became irritable and did not get along well with his family. On account of this, he left home and nothing was heard from him until June 5, when his wife was called to the Massachusetts General Hospital to see her husband. She was advised to take him to the Boston Psychopathic Hospital.

Here, the diagnosis of general paralysis was made on the history; neurologic signs, including Argyll-Robertson pupils; hyperactive reflexes; slurring speech; tremors of facial muscles; the mental symptoms of disorienation, poor memory, deterioration; and the serologic findings, which showed the following results: Wassermann reaction of blood serum, positive; Wassermann reaction of spinal fluid, positive; globulin, 3 +; cells, 15 per cmm.; total protein, 167 mg. per hundred cubic centimeters, and colloidal gold reaction 5554332000.

The patient was treated by malaria and allowed to have eight paroxysms. There was no improvement and the spinal fluid examination following the malarial treatment was but little changed.

August 28, he was inoculated intravenously with 0.1 cc. of blood.

September 6, the temperature rose to 104.6, and the next day was normal, making an incubation period of nine days. On the eighth day there appeared at the site of the intravenous inoculation at the bend of the right elbow an area of redness and induration the size of a half-dollar.

The patient was transferred to the Westboro State Hospital, September 11. He ran an irregular temperature (chart 3) until given eight intravenous injections of 0.3 Gm. of arsphenamine, following the first of which the temperature became normal and the disease was apparently cured.

DIAGNOSIS BY ANIMAL INOCULATIONS

The diagnosis of naturally acquired rat bite fever is usually a simple matter if there is a history of a bite followed by the development of lymphangitis, lymphadenitis, a relapsing temperature, and an exanthem. In atypical cases, or when there is no history of a bite, the disease probably is often not diagnosed. The demonstration of the causative organism is therefore of great diagnostic value. In two of the foregoing cases we endeavored to demonstrate the spirochete by the inoculation of experimental animals with blood taken from the patient. For these inoculation experiments we used mice and guinea-pigs. Both animals are very susceptible to the infection. We preferred guinea-pigs because the blood of these animals is normally free from spirochetes, whereas mice are often infected with a spirochete morphologically indistinguishable from the *Spirochaeta morsus-muris*. Before using our mice we therefore examined their blood by the dark-field several times to exclude a natural infection. Blood was withdrawn into a solution of sodium citrate in the usual manner from the patient's veins, and about a half-hour afterward inoculated either subcutaneously or intra-

peritoneally into animals. Whenever possible the animals were inoculated with blood taken as soon as the patient's temperature began to rise. Of six guinea-pigs inoculated with the blood from patient 1, only one developed typical signs of infection with spirochetes in the blood. This guinea-pig was injected subcutaneously with 2.5 cc. of the patient's blood taken on the seventeenth day after inoculation when the patient's temperature was rising at the commencement of his second paroxysm of the fever. The record of this guinea-pig is briefly as follows: One week after inoculation the guinea-pig showed an indurated area about 2 cm. long and 1 cm. wide at the site of injection. There was a well defined ulcer about 0.5 cm. in diameter over the center of the indurated area. Serum squeezed out of this ulcer was examined by the dark field, but no spirochetes were seen. The inguinal lymph glands became distinctly enlarged. On the fourteenth day spirochetes were first observed in the blood and gradually became more numerous on the succeeding days. This guinea-pig eventually developed the typical disease, with inflammation of the vulva and supralabial and circumocular alopecia. Blood from this guinea-pig was withdrawn on the thirty-ninth day and injected into patient 2 (chart 3).

The record of the guinea-pig that was inoculated at the same time and with the same amount of blood as the one described above is worth reporting. This animal likewise developed an indurated area at the site of inoculation and enlarged lymph glands. At no time, however, were spirochetes demonstrable in the blood. Mooser [15] has shown that *Spirochaeta morsus-muris* can produce a latent infection in guinea-pigs. That is, the guinea-pigs fail to develop clinical symptoms of the infection, but the organism can be recovered from them many weeks afterward by the implantation of the inguinal lymph nodes into other guinea-pigs. Unfortunately, Mooser's work was published too late for us to use his method to determine whether the guinea-pig described above was infected or not. On account of the fact that several of our guinea-pigs developed the same lesions, but at no time were spirochetes present in the blood, we feel that possibly in those cases we were dealing with a latent infection. Of the six guinea-pigs injected with blood from patient 1, one died a few days after inoculation, the one described above developed the typical disease, three developed enlarged inguinal lymph glands, and one remained entirely negative. Two of the guinea-pigs that developed what may be a latent infection were injected with blood taken on the second day of fever, when presumably the organisms were present in the patient's blood.

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15. Mooser, H.: Experimental Studies with a Spiral Organism Found in a Wild Rat, J. Exper. Med. **39**:589 (April) 1924; Experimental Studies with a Spiral Organism Found in a Wild Rat and Identical with the Organism Causing Rat Bite Fever, J. Exper. Med. **42**:539 (Oct.) 1925.

Two guinea-pigs that were inoculated with the serum expressed from the primary lesion of patient 1 remained negative. Of two mice injected with the fluid aspirated from the enlarged inguinal lymph gland, one developed the infection. Spirochetes were first seen in the blood of this mouse on the tenth day.

Seven guinea-pigs were inoculated with blood taken from patient B. Five of these remained in every respect normal. Two developed what is probably a latent infection, namely, an indurated area at the site of inoculation and enlarged lymph glands.

It will thus be seen that the diagnosis of sodoku by the demonstration of the causative organism either directly or by animal inoculation may be very difficult. Fortunately, there is a reliable serologic reaction. Futaki and his co-workers [10] have shown that when the blood serum from a convalescent patient with sodoku is mixed with blood containing *Spirochaeta morsus-muris,* the spirochetes immediately lose their motility and become disintegrated. During our rabbit experiments we became familiar with this reaction and convinced ourselves of the reliability of this test. The serums of all our patients were tested by this method and all showed spirocheticidal properties. In every case the spirochetes lost their motility in a few minutes and could no longer be found. The protocol of one of these tests follows:

Serum from patient 1 taken the day before he received an injection of arsphenamine was thoroughly mixed in a capillary pipet with an equal amount of guinea-pig's blood showing numerous spirochetes. This was immediately examined by the dark field. Three minutes after mixing most of the spirochetes were dead and the active movements of the remainder had ceased, each organism remaining at one spot and occasionally showing a convulsive movement. Seven minutes after mixing all the organisms were dead. The control in which normal serum was used showed active motility of the spirochetes for more than a half-hour after mixing.

The spirocheticidal action of the serum of patient 1 also was tested by means of Pfeiffer's phenomenon. A mixture containing 0.5 cc. of the patient's serum and 0.5 cc. of guinea-pig blood containing numerous spirochetes was injected into the peritoneal cavity of a guinea-pig. Small quantities of fluid were withdrawn from the peritoneal cavity at short intervals and examined under the dark field. In fluid withdrawn seven minutes after injection, only one motile spirochete was seen. Fluid withdrawn after this was always negative. In the control guinea-pig, which was injected the same way except that normal serum was used, there was no loss of motility after one hour.

RESULT OF TREATMENT

It is far too early to attempt to evaluate the therapeutic results of this treatment. At least several years must elapse with a considerable group of patients under treatment and observation. It is even too early to formulate the true value of the malarial treatment. This report is presented to call attention to the possibilities of this method of treatment in producing fever which can be used under circumstances similar to

those in which the malarial or relapsing fever methods have been advocated. However, we do feel justified in stating that clinical and serologic improvement has taken place in some of the patients treated by sodoku, a fact that is at least suggestive of the therapeutic value of the method.

SUMMARY

Sodoku is a disease produced by *Spirochaeta morsus-muris,* characterized by repeated attacks of fever, glandular enlargement and skin lesions, tending to spontaneous recovery after a period of weeks or months. Arsphenamine is apparently a specific therapeutic agent. Immune bodies are formed which offer a means of diagnosis by spirocheticidal tests. The organisms can be maintained in laboratory animals, e. g., rats, mice, guinea-pigs. On theoretical grounds it offers possibilities for the treatment of general paralysis similar to malaria and relapsing fever. Sodoku can be transferred to the human by either intradermal or intravenous inoculation of blood of an infected animal. The intravenous inoculation seems preferable because it avoids the formation of the primary lesion and lymphangitis which results from successful intradermal inoculation. The artificially produced disease is similar in its clinical manifestations to the naturally acquired disease, producing repeated paroxysms of fever of from 102 to 105 F., and is readily controlled by arsphenamine.

As a therapeutic method it has theoretical possibilities equal to malaria. In addition, there are a number of practical advantages over malaria. The organism can be maintained in laboratory animals and is thus always available for use, which obviates the necessity of transmitting human blood or having on hand a case of human infection. The disease is less debilitating to the patient than malaria. A further value is that it can be given to patients who are more or less immune to malaria. It is also available as an addition to the malarial therapy and may be given either before or after malaria without any evident modification of the clinical course of either condition.

ACUTE COCAINE POISONING AND ITS TREATMENT IN THE MONKEY (MACACUS RHESUS) *

A. L. TATUM, M.D.
AND
K. H. COLLINS, B.S.
CHICAGO

In a previous study of acute experimental cocaine poisoning and its treatment [1] we reported the following observations from experiments on the dog and the rabbit:

1. Death in acute poisoning from the hypodermic injection of cocaine hydrochloride is due to respiratory failure.

2. By the intravenous administration of appropriate hypnotics, e. g., barbital sodium (barbitalum soluble, U. S. P. X) with paraldehyde, the minimal lethal dosage of cocaine was raised from approximately 100 mg. per kilogram to 150 mg. per kilogram in the rabbit, and from approximately 26 mg. per kilogram to 65 mg. per kilogram in the dog. Convulsions ceased immediately during the injection of the hypnotics.

3. The convulsions caused by cocaine are largely of cortical origin; this disturbance contributes or is parallel to the more direct drug injury of the medullary centers, particularly the respiratory center. If the cortical manifestations of cocaine poisoning were controlled by hypnotics it was found that the medullary centers were far more resistant than in uncontrolled instances, thus accounting largely for the increased tolerance in acute poisoning.

4. The longer the convulsions are permitted to continue the greater is the danger of medullary failure.

5. Artificial respiration as a means of treatment of cocaine poisoning in the rabbit was quite satisfactory but entirely inefficient in the dog. Hence, in the higher mammal, the dog, asphyxia due to convulsions cannot be held responsible as the cause of death.

6. The dog was initially much more susceptible to cocaine poisoning than the rabbit and was correspondingly more amenable to hypnotic drug treatment, forming an interesting parallelism with or dependence on brain development.

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* From the laboratory of pharmacology of the University of Chicago.

* This work was supported in part by a grant from the therapeutic research fund of the American Medical Association.

1. Tatum, A. L.; Atkinson, A. J., and Collins, K. H.: Acute Cocaine Poisoning; Preliminary Report of Experimental Study, J. A. M. A. **84**:1177 (April 18) 1925; J. Pharm. & Exper. Therap. **26**:325, 1925.

In view of these facts the next logical step would naturally be a study of the same phenomena in still higher forms of life and for this purpose the monkey (*Macacus rhesus*) was chosen.

PROTOCOLS

EXPERIMENT 1.—Monkey; weight, 3.3 Kg.

10:26 a. m. Injected 40 mg. of cocaine hydrochloride per kilogram, subcutaneously.

10:30 a. m. Animal was delirious; wild.

10:40 a. m. Animal had tremors in the legs.

10:47 a. m. Animal had violent clonic convulsions.

10:48 a. m. Started intravenous injection of 70 mg. of barbital sodium per kilogram in 3.5 cc. of saturated solution of paraldehyde in saline solution per kilogram. Immediate cessation of convulsions; excellent muscle relaxation; deep sleep.

12:00. Beginning to waken.

1:10 p. m. Able to sit up.

1:30 p. m. Drinking water.

3:30 p. m. Ate a banana.

One month later the animal was still perfectly normal in appearance.

EXPERIMENT 2.—Monkey; weight, 5.6 Kg.

10:59 a. m. Subcutaneous injection of 60 mg. of cocaine hydrochloride per kilogram of body weight.

11:05 a. m. Animal had violent clonic convulsions.

11:07 a. m. Intravenous injection of 35.6 mg. of barbital sodium per kilogram in 1.75 cc. of saturated solution of paraldehyde in saline solution per kilogram. Immediate cessation of convulsions. Respiration stopped temporarily but returned on artificial respiration.

11:40 a. m. Animal apparently in excellent condition.

12:40 p. m. Tremors appeared in the legs.

12:45 p. m. Respiration was labored, then became weaker, finally ceasing altogether. Artificial respiration was maintained for over an hour, when the heart finally ceased beating.

2:00 p. m. Animal died.

EXPERIMENT 3.—Monkey; weight, 5.8 Kg.

9:50 a. m. Injected subcutaneously 60 mg. of cocaine hydrochloride per kilogram of body weight.

9:55 a. m. Animal had violent clonic convulsions.

10:01 a. m. Gave 70 mg. of barbital sodium per kilogram in 3.5 cc. of saturated solution of paraldehyde in saline solution per kilogram. Immediate cessation of convulsions; deep sleep.

11:45 a. m. Beginning to waken.

12:05. Running about but with poor muscle coordination. Ate food later in the day.

Complete and lasting recovery.

EXPERIMENT 4.—Monkey; weight, 4.2 Kg.

10:31 a. m. Injected subcutaneously 80 mg. of cocaine hydrochloride per kilogram of body weight.

10:36 a. m. Animal had violent clonic convulsions.

10:38 a. m. Injection of barbital paraldehyde solution in same dosage as in Experiments 1 and 3, intravenously. Immediate cessation of convulsions; sound sleep.

12:46 p. m. Beginning to waken.

3:20 p. m. Animal was rather unsteady on his feet but ate a banana.

Permanent and complete recovery.

EXPERIMENT 5.—Monkey; weight, 2.9 Kg.

9:30 a. m. Injected 40 mg. of cocaine hydrochloride per kilogram, subcutaneously.

9:39 a. m. Animal had severe clonic convulsions. No treatment was given. Animal had convulsions with intervals of relative quiet during which periods the respiratory movements became more rapid and shallow.

9:55 a. m. Animal died.

EXPERIMENT 6.—Monkey; weight, 3.6 Kg.

10:36 a. m. Injected subcutaneously 100 mg. of cocaine hydrochloride per kilogram.

10:40 a. m. Animal had violent clonic convulsions.

10:41-43. Intravenous injection of the same dosage of barbital sodium and paraldehyde as in Experiments 1, 3 and 4. Immediate cessation of convulsions; deep sleep.

1:21 p. m. Began to waken.

1:40 p. m. Animal raised his head and looked about.

2:04 p. m. Animal was replaced in his cage.

Complete recovery in a few hours.

EXPERIMENT 7.—Monkey; weight, 2.2 Kg.

10:52 a. m. Injected subcutaneously 30 mg. of cocaine hydrochloride per kilogram.

11:20 a. m. Animal had violent convulsions.

11:44 a. m. Animal died by respiratory failure.

EXPERIMENT 8.—Same animal as used for Experiment 4 one month later; weight, 4.6 Kg.

9:30 a. m. Injected 20 mg. of cocaine hydrochloride per kilogram, subcutaneously.

9:42 a. m. Animal was wild and delirious. No signs of convulsions at any time. Recovery uneventful.

Condensation of Results

Animal	Cocaine Hydrochloride, Mg. per Kg.	Treatment		Results
		Barbital Sodium, Mg. per Kg.	Saturated Solution of Paraldehyde Cc. per Kg.	
8	20	..	...	Recovery
5	40	..	...	Death
7	30	..	...	Death
1	40	70	3.5	Recovery
2	60	35.6	1.75	Death
3	60	70	3.5	Recovery
4	80	70	3.5	Recovery
6	100	70	3.5	Recovery

It is evident from a study of the accompanying table that the minimal lethal dose of cocaine hydrochloride administered subcutaneously to the rhesus monkey is approximately 30 mg. per kilogram of body weight. How much less would have been fatal we do not know but we believe that for purposes of calculation the minimal lethal dose is safely considered to be below 30 mg. per kilogram.

Since animal 6, receiving 100 mg. of cocaine hydrochloride per kilogram, recovered on treatment, we believe the upper limit had not been reached. However, on the basis of 100 mg. per kilogram being a dose from which recovery is safely obtained, we are justified in saying that the minimal lethal dosage *with* treatment after convulsions

are well established is well over three times the minimal lethal dose in the untreated animals.

Animal 2 well illustrates a point emphasized in our earlier paper; namely, that it is absolutely necessary to give enough of the hypnotics to prevent all evidences of cortical stimulation. The dosage of the barbital paraldehyde mixture was in this instance too small because muscle twitchings and mild tremors developed some time after the antidote had been administered. The death of this animal we attribute largely to incomplete control of the cortical stimulant action of cocaine affecting in a harmful manner the injured respiratory center. We fully realize, however, the possibility of the hypnotics antidoting the actions of cocaine on the midbrain or the medulla as well as on the cortex.

Hofvendahl[2] in 1922 reported a single experiment on the monkey poisoned by 80 mg. of cocaine hydrochloride per kilogram of body weight, then treated by use of a barbituric acid derivative. The animal recovered. A month later the same animal was killed by 40 mg. of cocaine hydrochloride per kilogram. This experiment by Hofvendahl together with our eight experiments supported by the foundations laid in our experiments on rabbits and dogs, we believe fully justify our conclusions.

Artificial respiration alone is quite satisfactory in the treatment of cocaine poisoning in the rabbit but quite futile in the dog and evidently also in the monkey (animal 2). Hypnotic drug treatment of the poisoning was, on the contrary, progressively more successful in the higher mammals, dog and monkey. These facts we believe indicate a progressively increasing controlling influence on the higher centers of the brain on the medullary centers with the increasing complexity of the brain.

Since the experiments on the dog were more favorable than on the rabbit and the experiments on the monkey, in turn, were more favorable than those on the dog, it follows that acute cocaine poisoning in man should be correspondingly more effectively treated by the same general method.

SUMMARY

1. Acute cocaine poisoning in the rabbit, dog and monkey has been proved to be readily and satisfactorily treated by appropriate hypnotics (barbital sodium with paralydehyde[3]) administered intravenously.

2. Hofvendahl, A.: Ztschr. f. Hals-, Nasen- u. Ohrenh. **1**:233, 1922.

3. It may be of interest to note that solutions of barbital sodium and paraldehyde are quite stable; hence they may be prepared as stock solutions for use in emergencies.

2. A proper dosage of the hypnotic, given intravenously, causes immediate cessation of cocaine convulsions in the monkey, dog and rabbit, and maintains depression for a time sufficient to allow more or less complete detoxication of cocaine to occur.

3. Manifestations of cortical stimulation must be absolutely controlled by a proper dose of the hypnotics; otherwise, the cerebral stimulus from cocaine so affects the cocaine poisoned medullary centers as to lead to their complete failure.

4. The higher the type of animal employed the greater is the difference between the minimal lethal dose in the untreated animal and the dose recovered from when treated by the hypnotic drug method.

5. We believe that man, being of a still higher order, would therefore be still more subject to successful treatment of acute cocaine poisoning by the use of the proper hypnotics.

CORRECTION

STENOSIS OF THE ISTHMUS (COARCTATION) OF THE AORTA AND ITS DIAGNOSIS DURING LIFE

JOHN T. KING, JR., M.D.

In the third paragraph of this article, published in the July issue of the ARCHIVES OF INTERNAL MEDICINE, an error was made in referring to the cases analyzed by Dr. Abbott in 1915. The number should have read 212, instead of twelve.

Book Reviews

DISEASES OF THE HEART. By DR. HENRI VAQUEZ, Professor of the Faculty of Medicine of Paris, Physician to L'hospital de la Pitie, Member of the Academy of Medicine (Paris). Translated and edited by GEORGE F. LAIDLAW, M.D., Associate Physician to the Fifth Avenue Hospital, New York City, Fellow of the Academy of Medicine of New York. Introduction by WILLIAM S. THAYER, M.D., F.R.C.P.I. (HON.) Professor Emeritus of Medicine, Johns Hopkins University, Visiting Physician to the Johns Hopkins Hospital, Baltimore, Associate Foreign Member of the Academy of Medicine (Paris). Pp. 743. Philadelphia: W. B. Saunders Company, 1925.

This work is a rather thorough exposition of diseases of the heart and consists largely of the personal views of the author.

The points of especial excellence are the vivid clinical pictures that the author portrays, the section on congenital heart disease, and the discussion of the arrhythmias. Also, in the discussion of electrocardiography the author has succeeded in keeping on safe middle ground, avoiding the Scylla of over-optimism and the equally undesirable Charybdis of total disappointment.

The portion of the book dealing with endocarditis shows a wide divergence of opinion from that entertained today by most British and American cardiologists. The total disregard of the later reports on rheumatic heart disease and streptococcus endocarditis shows that the author has failed to be convinced by these reports.

Some of his statements are surely open to question. It is doubtful if simple benign endocarditis and infectious endocarditis may be as sharply differentiated as he does it. Surely, in those cases in which the streptococcus is recovered from the blood the prognosis is not as bad as he pictures it, nor are the organisms as difficult to recover as he would lead us to believe. He confesses the inadequacy of drug therapy, but does sufficiently stress the most valuable therapeutic agent at our command, namely, rest in bed.

The same difference of opinion is exhibited in dealing with valvular disease. One is left under the impression that if the valves are once damaged, the failure of the heart must be progressive. This question has not yet been satisfactorily answered. Certainly, the effect of active infection and recurrent infection has not been sufficiently emphasized by the author and many cardiologists will state that in the absence of infection the damaged heart will deteriorate no more rapidly than the undamaged heart.

In that portion of the book devoted to angina pectoris, the sharp differentiation between angina pectoris of effort and that of decubitis is somewhat questionable. The case in which the anginal attack appeared coincidently with a demonstrable dilatation of the heart is an exceedingly interesting one, if the observation is accurate. Mention of the purin base diuretics in angina or the employment of surgical procedure for the relief of pain is lacking.

Advocacy of vigorous arsenical therapy in the treatment of cardiovascular syphilis will not meet with universal approbation. Rather convincing proof has been offered to support the view that such procedure is not without very real danger.

In the consideration of the cardiac arrhythmias sinus irregularity has been relabeled the youthful type of arrhythmia. It is, of course, common enough in all ages and its incidence in old age is but little exceeded by that in youth.

A discussion of quinidine occupies most of the treatment of auricular fibrillation. Digitalis is mentioned only as a preliminary measure to restore normal rhythm. A therapeutic measure as efficient as digitalis in the treatment of

auricular fibrillation should be given more consideration in a discussion of the treatment of this condition. The statement that "quinidine may be given with advantage to all patients suffering from complete arrhythmia" should not go unchallenged even though the author qualifies this by later presenting a list of contraindications. The existence of active endocarditis is such an absolute contraindication that the original statement should never appear without immediate qualification.

The book as a whole exhibits the enormous extent of the author's work and, in most instances, the accuracy of his observation. It is the result of painstaking effort and the minutest attention to detail. No subject escapes the closest scrutiny. The value of the book is further enhanced by an excellent bibliography. It provides a valuable addition to any library on diseases of the heart.

Lastly, the translator should be highly commended for his work in preserving the vividness of the clinical portrayals.

PHYSICAL DIAGNOSIS OF DISEASES OF THE CHEST. By PRATT and BUSHNELL. Price, $7.50. Philadelphia: W. B. Saunders Company.

This book was written as the result of experiences in teaching physical diagnosis to medical officers of the Reserve Corps in the late war. That work demonstrated that many physicians were lamentably unskilled in methods of examination and in interpretation of examinations, and the writers of this volume begin with fundamentals—physical laws of sound formation and transmission—apply these to normal cases and later compare the deviations from normal with their causes and interpretations.

Palpation, percussion, auscultation, resonance and fremitus are considered, first in normal, later in pathologic cases, with separate chapters devoted to diseases of the lungs and pleura and a special chapter on pulmonary tuberculosis.

The physiology and anatomy, normal and abnormal, of the heart are considered; next, general procedures of diagnosis, inspection, palpation, percussion and auscultation of the heart, with discussion of normal and abnormal observations as well as of information to be gained from the condition of the blood vessels. A chapter on instrumental methods of diagnosis includes use and interpretation of blood pressure examinations, venous pressure, the sphygmogram, phlebogram, electrocardiogram, orthodiagram and teleradiogram.

The cardiac irregularities, valvular disease and myocarditis are carefully considered, as well as pericardial and aortic disease. Especially instructive is the chapter on cardiac neuroses; though short, it gives valuable help in their detection.

The cardiac portion of the book is commendable, as any well written treatise on the subject is, but the section on pleural and pulmonary diagnosis is especially well done and deserves widespread study on the part of the general clinician.

MEDICAL DIAGNOSIS. By JAMES M. ANDERS and LEONARD NAPOLEON BOSTON. Price, $12. Philadelphia: W. B. Saunders Company.

This is the third edition. It retains the general plan of the widely used second edition but is entirely reset and brought up to date with reference to newly described diseases and methods. Description of cases has been omitted to give space to a more comprehensive discussion of diagnosis.

The volume emphasizes throughout with diagnostic and differential tables the features of the condition discussed, both clinical and laboratory. The correlation between clinical manifestations and the structural changes, as well as special etiologic factors of infection, are also discussed.

The volume is a well conceived, carefully executed text containing in not too brief form all that can be included in any single book.

INVESTIGATIONS INTO THE MORPHOLOGY OF THE RAY FUNGI. By J. ORSKOV, the State Serum Institute, Copenhagen. Pp 171. Copenhagen: Levin and Munksgaard, 1923.

This monograph is a cultural and morphologic study of certain of the ray fungi. These are compared with the corynebacteria and mycobacteria. Certain criteria are given for a new classification and nomenclature of the fungi. The close resemblance of certain corynebacteria and mycobacteria to the fungi is considered. The monograph is of use chiefly to bacteriologists as a reference.

STUDIES OF GONOCOCCUS TYPES AND GONOCOCCUS IMMUNE SERUMS. By ERIK VOLLMOND. Pp. 187. Copenhagen: Levin and Munksgaard, 1923.

Because of divergent results obtained with the complement fixation test in gonorrhea regardless of the clinical course of the infection, Erik Vollmond, in consideration of these results, presumed that the gonococcus, like the meningococcus and other bacterial species constitute a heterogeneous family, comprising types with different antigenic properties. He believes, as the result of serologic studies, that most gonococcus strains can be arranged in three types (I, II and III). The type I infection is less severe than the other two.

CLASSIFICATION OF THE STRAINS BELONGING TO THE TYPHOID-PARATYPHOID GROUP OF BACTERIA TOGETHER WITH A DEMONSTRATION OF DIFFERENCES IN AVIDITY. By A. HECHT-JOHANSEN. Pp. 207. Copenhagen: Levin and Munskgaard, 1923.

The first part of this monograph is a serologic study of approximately 100 strains of the typhoid-parathyphoid-enteritides group of bacteria in an attempt at classification. On the basis of results obtained the author divides these strains of bacteria into eleven groups, some large, others small. The second part is a study in avidity and the author finds a marked unequality with which bacterial strains bind immune substance. The chief value of this monograph is as a reference for bacteriologists or immunologists interested in these problems.

STUDIES ON THE PAPILLAE VALLATAE OF MAN. By DR. AUGUST JURISCH. Pp. 157. Munich: J. F. Bergmann. Berlin: Julius Springer, 1922.

This is a comprehensive historical review and histologic study of the papillae vallatae of the human tongue. Its chief value is to anatomists and histologists. There are numerous tables, charts, drawings and photographs. One chapter concerns the foramen caecum and the sulcus terminalis.

FOOD FOR THE DIABETIC. By MARY PASCOE HUSSLESON. New York: MacMillan Company.

The first edition of this little volume filled a definite need and ranked among the best of the many little books on diabetes. The slight revisions of the second edition make this new printing more valuable.